Platelet transfusions and patient outcomes after cardiac surgery

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CHAPTER 7

General discussion

Aim of this thesis

The overall goal of this thesis was to expand knowledge about the safety and efficacy of platelet transfusions in general and in particular in cardiac surgery patients by studying the influence of the administration of one unit of platelets, the influence of storage medium and storage time on clinical outcomes of patients. Expansion of knowledge about this topic creates possibilities to further improve the safety and efficacy of platelet transfusions.

The first issue this thesis addresses is whether certain characteristics of a platelet unit influence its efficacy and safety. In hematology patients, it has been suggested that reducing the amount of plasma in platelet units could diminish 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 this thesis we compared the occurrence of transfusions reactions in all patients transfused with PAS-B-platelets, PAS-C-platelets, or plasma-platelets in routine clinical use.

Besides a possible difference between PAS and plasma-platelets regarding safety, and in particular transfusion reactions, also efficacy is of major concern. It is unclear whether PAS-platelet concentrates are as effective as plasma-platelet concentrates. In our *in-vitro* study we compared the hemostatic function of PAS-platelets to plasma-platelets in reconstituted whole blood. The hemostatic function was measured using Multiplate-derived platelet aggregation and TEG-measured overall clot formation.

Apart from storage medium also the storage time of platelet concentrates is of interest with regard to safety and efficacy of platelet transfusions. Increased storage time has been associated with the accumulation of biological response modifiers, such as inflammatory cytokines and chemokines.(1-4). Whether these changes also have clinical consequences is not clear yet, as published results on this matter are contradictory.(5, 6) This controversy indicates that a better understanding of the influence of storage time on safety and efficacy is needed and will create an opportunity to further improve the effect of platelet transfusions. Therefore, we assessed whether there is an association between the storage time of platelet units and transfusion reactions.

In addition to the characteristics of the platelet concentrate, it is plausible that also the patient characteristics and the underlying clinical situation necessitating platelet transfusion may influence its effect. Since a significant proportion of all platelet transfusions is consumed by cardiac surgery patients, it is important to understand the effect of a platelet concentrate and its storage conditions on cardiac surgery patients. There is a lack of clinical evidence establishing the hemostatic effectiveness of platelet transfu-

sions in cardiac surgery patients.(7) In addition, conflicting results have been reported regarding the safety of platelet transfusions in the setting of cardiac surgery.(8-14) Consequently, there is an unmet need to determine the clinical impact (safety and efficacy) of perioperative platelet transfusions in patients undergoing cardiac surgery. Therefore, we studied the efficacy and safety of platelet transfusion following cardiac surgery by comparing patients who have received a platelet transfusion with propensity-score-matched patients who did not receive a transfusion.

Subsequently, the question arose whether storage time of platelet concentrates has a clinically significant impact in transfused cardiac surgery patients. As mentioned above, *in vitro* studies show that during storage platelets undergo multiple changes in structure and function collectively known as the "platelet storage lesion".(15, 16) It is conceivable that in patients this "platelet storage lesion" results in a reduced hemostatic capacity and more adverse events.(17-19) Hence, we evaluated whether platelet storage time is associated with efficacy and safety outcomes in cardiac surgery patients receiving platelet transfusions.

Discussion and considerations for future research

Part I: Platelet transfusions in general

Impact of storage medium on safety and efficacy

One of the most important findings in our study, in chapter 2, is that PAS-C-platelets are associated with less transfusion reactions than plasma and PAS-B platelets. This result is based on a nationwide database comprising all reported transfusions reactions of a period of 10 years, representing the whole patient population transfused with platelet concentrates in this time frame. The geographical determined distribution of storage media within the Netherlands provided a unique opportunity to compare the storage media within one country. In contrast to most previous studies, the advantages of this setting are that the different storage media are used in comparable populations, during the same time period, within the same healthcare system with the same protocols and the same hemovigilance system. The database covers over half a million platelet transfusions, enabling the analysis of less common reaction types like anaphylactic reactions, TRALI, and TACO separately. Moreover, the overall incidence of reported reactions in our study is relatively high compared to other countries with passive surveillance. The incidence of RBC transfusion reactions is also relatively high which is probably indicative of the accuracy of the Dutch hemovigilance system. The considerable size of our study population made it possible to estimate the effect of storage medium on the incidence of transfusion reactions with more certainty and accuracy than previous studies.

In our *in vitro* study, in chapter 3, we observed that the aggregation and the agonist induced CD62P responsiveness of PAS-C-platelets was lower than the aggregation of plasma–platelets. However, TEG-derived clot formation, showed no differences between the PAS-C-platelets and plasma-platelets. This might suggest that the decreased platelet aggregation does not result in impaired overall clot formation. However, another possibility is that TEG is (partly) insensitive to differences in platelet function. In viscoelastic testing the applied activators give rise to a thrombin burst that can bypass and thereby hide dysfunction of adenosine diphosphate receptors by activating protease-activated receptors (PAR).(20)

Besides the lower platelet function of PAS-C-platelets compared to plasma-platelets, also the fluid in which the platelets are stored may be an issue of concern. While plasma-platelets are stored in donor plasma containing coagulation factors, in PAS-platelets most of the plasma is replaced by PAS-fluid, which does not contain coagulation factors. In case of massive transfusion the lower concentration of coagulation factors in PAS-C could pose a problem, as was also discussed in the 2015 review of Dudaryk et al.(21) We propose that future research should compare the clinical (bleeding related) outcomes of massive transfusions with PAS-platelets to massive transfusions with plasma-platelets. An advantage of performing such a study retrospectively with Dutch data is that PAS and plasma stored platelets were used concurrently in the Netherlands.

Impact of storage time on safety and efficacy of platelets

Our study, in chapter 4, exploring the effect of storage time on transfusion reaction rates was performed on a large nationwide database, comparable to the database used for the storage medium (see previous paragraph).

We demonstrated that in contrast to plasma stored platelets, in PAS platelets, storage time is associated with a higher incidence of transfusion reactions. However, the overall incidence of transfusion reactions, so regardless of storage time, following plasma platelets is higher than that of PAS-C platelets.

Besides the safety aspect of platelet transfusions, obviously the intended hemostatic efficacy should also be considered. Both PAS-platelet and plasma-platelets showed an increase in baseline CD62P expression, indicating baseline activation, with increasing storage time. Also, a decrease in CD62P responsiveness over storage time was observed. In another study a correlation was observed between platelet responsiveness (TRAP induced) and 1-hour corrected count increment (CCI).(22) The CCI is the increase in circulating platelets corrected for the administered dose and the blood volume of the patient and is often used for hemato-oncological patients. Despite being a poor surrogate marker for bleeding tendency,(23-25) CCIs are associated with the time to next

transfusions and are therefore of clinical relevance (26). Whether the decreasing CD62P responsiveness over storage time is also associated with hemostatic efficacy parameters in (cardiac) surgery patients is unknown.

Furthermore, both in plasma-platelets and in PAS-platelets (Multiplate-derived) *in vitro* aggregation (TEG-derived) initial clot formation significantly declined with an increasing storage time, but (TEG-derived) maximum clot strength and clot growth rate did not decline with increasing storage time. Furthermore, In previous studies, Multiplate results have been shown to be correlated to bleeding and thromboembolic complications in patients undergoing coronary stenting and cardiac surgery.(27-29)

Evidently, further research is needed to explore whether the changes we observed *in vitro* also cause changes in clinical practice, where other factors like blood flow, vascular endothelium, other blood components, and patient factors influence hemostasis and outcomes. The potential effect of storage time of could be different in different patient populations, so these clinical studies should be performed in separate populations receiving platelet transfusions.

Part II: Platelet transfusions in cardiac surgery patients

Impact of a platelet transfusion on safety and efficacy

In addition to the characteristics of the platelet concentrate, it is plausible that also the patient characteristics and the clinical situation influence the effect of a platelet transfusion. To the best of our knowledge, our study in chapter 5 is the first paper 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. 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. However, early platelet transfusion was not associated with reinterventions, thromboembolic complications, infections, multi-organ failure, or mortality.

In contrast to other studies we analyzed patients receiving only one platelet unit and no other blood product shortly after the end of cardiopulmonary bypass(CPB). We selected these patients because in these patients the indication for the platelet transfusion varies between physicians. As a result, patients receiving one unit and those receiving no units have more or less similar clinical characteristics, which reduces the chance of confounding-by-indication. In addition, we used propensity score matching to identify

the patients, who received no transfusion who were most comparable to the patients transfused with a platelet concentrate and thereby reduce the potential remaining confounding even further. Furthermore, our data were collected prior to and therefore independently of our analysis, minimizing information and selection bias. However, larger studies are necessary to estimate the impact of platelet transfusions in cardiac surgery patients. Ideally, future research should prospectively compare a restrictive with a liberal platelet transfusion policy.

Indication for a platelet transfusion in cardiac surgery

Besides the impact of a platelet transfusion in cardiac surgery, the exact indication for platelet transfusion in cardiac surgery patients should also be established. Transfusing the right patients at the right time, is an essential and challenging part of transfusion medicine. In cardiac surgery there is a lack of guidance on platelet transfusion. To our knowledge, there are no randomized controlled trials about the safety and efficacy of platelet transfusions in cardiac surgery.(30) The scarcity of evidence to guide the use of platelets in cardiac surgery contributes to the significant variability in transfusion practice in cardiac surgery patients.(31-33). The American Association of Blood Banks (AABB), EACTS/EACTA and STS/ACS guidelines provide recommendations based on low-quality evidence and the existing guidelines provide little concrete insights with respect to the treatment of postoperative bleeding when (likely) related to platelet dysfunction. The EACTS/EACTA guidelines propose that platelet concentrate should be transfused in bleeding patients with a platelet count below 50, 000 cells/μL or under antiplatelet therapy (class IIa, level C).(34) According to the STS/ACS guidelines the decision to transfuse non-red cell hemostatic blood products should be based on clinical evidence of bleeding and preferably guided by point-of-care tests that assess hemostatic function in a timely and accurate way. (class IIA, level of evidence C).(30) However, neither specific tests nor specific values for platelet dysfunction are advised. Accordingly, as was observed in a study evaluating the changes in clinical practice as a result of the guidelines, the influence of the (STS/ACS) guidelines on daily patient care is limited. (35) The authors suggested several possible explanations, including "practitioner views of outside control of clinical practice, low level of strength of the evidence supporting a given recommendation, appropriateness and usefulness of the specific guidelines, and availability of resources to implement the guidelines". So, currently the indication for platelet transfusions is still significantly influenced by the institution, the physician and other subjective, immeasurable factors such as the surgeon estimation of excess bleeding and (previous) antiplatelet medication use by the patient without an actual measurement of the platelet function.(31) The resulting under- and overutilization of platelet transfusions in cardiac surgery should be avoided because underutilization can lead to unnecessary blood loss and associated morbidity and overutilization will lead to unnecessary adverse events and costs.

POC tests and transfusion algorithms in cardiac surgery

In the STS/ACS guidelines "a multimodality approach involving multiple stakeholders, institutional support, enforceable transfusion algorithms supplemented with point-of-care testing, and all of the efficacious blood conservation interventions" as this 'will limit blood transfusion and provide optimal blood conservation for cardiac operations" (class I recommendation, level of evidence A). The rationale for this recommendation is based on a number of studies prospectively analyzing transfusion algorithms in institution-derived transfusion practices in concurrence with accurate point-of-care (POC) testing to handle bleeding and to guide blood transfusion. Most of the mentioned studies (36-41), including two RCTs, showed that the use of POC testing and transfusion algorithms resulted in improved hemostasis and in fewer transfusions. Also the EACTS/EACTA guidelines recommend to implement a patient blood management protocol (class I, level of evidence C). Additionally, the use of perioperative POC tests should be considered to reduce the transfusion requirements (class IIa, level B). The STS/ACS guidelines also mention that it is not clear whether the algorithms guiding transfusion and the multidisciplinary approach are more important than the POC testing. Thus, available evidence supports both the use of transfusion algorithms and POC assays to guide transfusion practice and improve blood conservation.

Platelet function tests in cardiac surgery

Furthermore, it was noted that most of the published studies included only viscoelastic coagulation tests, although a specific platelet function test was included in the algorithm in 2 of the more recent studies.(42, 43) Additionally, a systematic review and meta-analysis observed that POC platelet function tests can indeed detect platelet dysfunction in cardiac surgery patients. And that the platelet function tests showed significant variability in their ability to predict blood loss and transfusion requirements. According to Bolliger et al the low predictive value can partly be explained by the fact that the etiology of bleeding after cardiac surgery is commonly multifactorial.(44)

Moreover, the implementation of a platelet function test into a blood management protocol was associated with reduced blood loss and red blood cell and plasma transfusion demands. The review also states that the combination of viscoelastic and other platelet function testing methods achieved a larger effect size in terms of blood loss reduction than viscoelastic methods alone. Also, it was shown that the combination of viscoelastic and platelet function testing results in less red blood cell transfusions than with viscoelastic testing alone. However, for platelet transfusions it was the opposite: viscoelastic testing alone resulted in less platelet transfusions than the combination of viscoelastic and platelet function testing.(45) A more recent narrative review about POC platelet function testing stated that for clinical use, cut-off values to define high postoperative bleeding risk or increased risk for ischemic events definitively need to be

better validated. In addition, it concludes that studies evaluating the value of platelet function tests in clinical decisions in bleeding patients after cardiac surgery are sparse. Thus, this review does not yet recommend a common and widespread use of perioperative platelet function testing.

Concluding, it is not undisputed whether POC platelet function tests should be part of blood conservation and transfusion algorithms / protocols. Currently there are a couple of POC platelet function tests that are fast and affordable,(46) but both the international guidelines and the earlier mentioned review papers cannot recommend a specific platelet function test. Future research should determine whether one platelet function POC test is preferred over the others.

On top of that clinically relevant cut-off values have to be established for cardiac surgery patients. The PLATFORM study found that platelet function tests with multiple electrode aggregometry after cardiopulmonary bypass are significantly associated with postoperative bleeding. The study also showed that the ADP-test had the best discrimination and which cut-off value had the best predictive value for postoperative blood loss. (29) More of these type of studies are needed to establish the most accurate platelet function test and the best cut-off values. Once proper cut-off levels for non-acceptable intraoperative and postoperative platelet function are established, POC platelet function tests can actually be added to guidelines, protocols and daily clinical practice.

Another important aspect that needs attention is the dosing of platelet transfusions. In an *ex vivo* study exploring how many platelet units are necessary to undo the clopidogrel effect, the equivalent of five units, was not even sufficient to achieve normal platelet aggregation under flow conditions.(47) As *in vitro* platelet aggregation is strongly correlated with postoperative hemorrhage it is possible that the finding of this study indicates that transfusion with one unit of platelets for patients on antiplatelet drugs is insufficient to correct the bleeding disorder. Future research is required to evaluate the optimal dose of platelet units in certain clinical situations. Concurrently, obviously surgical techniques and surgical tools that reduce the surgical tissue injury and thereby the need for transfusions should continuously be developed and improved.

Impact of storage time on safety and efficacy

In our study in chapter 6 we evaluated in cardiac surgery patients whether storage time of transfused platelet concentrates was associated with adverse outcomes. The most important finding of this study was that, in our cardiac surgery population, transfusion of old platelets was associated with a higher in-hospital mortality when compared to transfusion of fresh 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.

We selected cardiac surgery patients who received solely old platelets or solely fresh platelets. That enabled a clear comparison without the influence of exposure to both types of platelets. Differences in outcomes between patients exposed to platelets with different storage time may have been due to other risk factors for the outcome. Yet, clinical decisions to transfuse fresh or old platelet concentrates were made independently from the storage time of the platelet concentrates, as the treating physicians was not aware of and could not influence the storage time of the transfused concentrates. Platelets are issued according to the first-in-first-out principle. Therefore, the storage time can be influenced by the number of platelets a patient receives, because the more concentrates a patient receives, the bigger the chance that that patient will receive a fresh concentrate (as these concentrates lie in the back of the shelf). Therefore, patients with unfavorable risk profiles and worse prognosis tend to receive more platelet concentrates with a higher chance of receiving fresher platelets. To minimize this potentially confounding factor of the amount of platelet transfusions, our analyses were corrected for number of platelet transfusions administered. Even if residual confounding is left despite the correction, then we expect it to result in an underestimation of the actual effect, because the patients with a less favorable prognosis received younger platelets then the patients with a better prognosis. The analyses were also corrected for logistic EuroSCORE, age, gender, left ventricular function, recent myocardial infarction, isolated CABG, and hospital. EuroSCORE is an internationally accepted scoring system for the prediction of early mortality in cardiac surgical patients (in Europe) on the basis of objective preoperative risk factors.(48) So by correcting for EuroSCORE factors that are considered relevant for early mortality in cardiac surgery are taken into account. We therefore conclude that it is unlikely that bias or confounding explain our findings.

To the best of our knowledge there is only one other study that investigated the association between storage time of platelets and clinical outcomes of cardiac surgery patients. (49) In contrast to our study, this study did not find an association between storage time of platelets and post-cardiac surgery adverse outcomes. A possible explanation for the difference between the findings is that the study of Welsby et al only contained nonemergent CABG patients transfused with apheresis platelets with a maximum storage of 5 days while our study included both elective and non-elective cardiac surgery patients transfused with pooled buffy-coat platelets with a maximum storage of 7 days. So our database contains more high-risk patients who might also be more vulnerable for the potential influence of transfusion with old platelets. This difference in risk-profile of the patient populations is also reflected in the hospital mortality (of 5.2%) observed by Welsby et al, that is lower than the hospital mortality we observed (9.0%). Besides,

possibly the "platelet storage lesion" is different in apheresis than in pooled platelets and more importantly the two days longer maximal storage time in our pooled platelets might lead to more "storage lesion". Our main analysis contained a larger population and more importantly our population consisted of patients transfused solely with old or solely with fresh platelets to avoid dilution of the association.

Our findings suggest that in-hospital mortality, postoperative (first 12 hours) blood loss >1000 mL and reoperation for bleeding occur more frequently following transfusion of old platelets. Based on these results the most obvious potential explanation for the higher hospital mortality are the higher blood loss and the resulting higher need for reoperation. If this is the actual explanation for the higher hospital mortality after transfusion with old platelets, this would suggest that old platelets are less effective in preventing and/or stopping bleeding in cardiac surgery. This possible explanation for our findings is plausible in the light of the discoveries earlier studies showed: the increase of platelet activation, while responsiveness to agonist decreased and a decline of platelet viability and function, together called the "platelet storage lesion".(5, 15, 50-54) Besides the possibly reduced efficacy of old platelets compared to fresh platelets, other possible (partial) explanations of the higher in-hospital mortality could be a higher risk of TRALI, other transfusion reactions or other complications that was observed with longer storage of platelets.(55-58)

The possible clinical implication of these results is that cardiac surgery patients are transfused with fresher platelet products as compared with current practice. Yet, this is just one study, with a study design that is suboptimal with respect to minimization of bias. Therefore, we feel that future studies should first confirm or refute the findings of the current study. In conclusion, in our cardiac surgery population transfusion of old platelets was associated with a higher hospital mortality, more blood loss and more reoperations for bleeding compared to fresh platelets. In our opinion these results instigate further research into this topic because if old platelets actually do cause higher hospital mortality in cardiac surgery patients this asks for a change in clinical practice.

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