# Platelet transfusions and patient outcomes after cardiac surgery

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CHAPTER 1

# 1

# General introduction and outline of this thesis

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## Part I: Platelet transfusions in general

***Platelet transfusions***

Platelet transfusions are used to provide hemostatic capacity to patients with decreased number or functionality of platelets.[1] In the Netherlands pooled platelet concentrates are prepared using five AB0 identical and Rh-D compatible buffy coats from whole blood donations and the remaining 10% of platelet units are collected by apheresis.[2] The five buffy coats for the pooled platelet units, each containing 25 mL of plasma, are resuspended either in 100% plasma of one of the five donors (plasma-platelets) or in 60-70% platelet additive solution (PAS) and 30-40% plasma (PAS-platelets).

***Storage medium***

PAS is a saline based crystalloid developed for the storage of platelets.[3] During this execution of this thesis PAS and plasma were used concurrently as storage medium for platelets in the Netherlands. In which storage medium platelets were stored was determined by the geographic location of a hospital. In the region South-West platelets were stored in PAS and in the other regions platelets were stored in plasma. Up to 2012 PAS-B fluid (T-sol, Baxter) and since 2013 PAS-C (Intersol, Fenwal, Inc)was used. In PAS-C phosphate is added as an extra buffer compared to PAS-B.[4]

PAS was developed to replace part of the plasma from platelet concentrates because of the considered harmful effect on platelets of enzymes in plasma.[5] Furthermore, with PAS it is possible to optimize the storage conditions, especially by increasing the buffer capacity and with that improving platelet quality.[6] Platelets use oxidation of glucose for energy supply which results in ATP and lactic acid which causes lowering of the pH. Lowering of the pH induces (more) platelet activation and thereby more glucose oxidation and resulting lactic acid production, which forms a vicious circle. Most types of PAS contain acetate as energy source for platelets to reduce the oxidation of glucose into lactic acid. Metabolism of acetate results in the formation of bicarbonate, which forms an extra buffer to stabilize the pH. All PAS-platelet units still contain 20-35% of plasma as source of glucose and to maintain platelet membrane integrity.[3,4,7]. In addition, several studies have suggested that cytokines and other substances present in the plasma fraction of platelet units play an important role in the etiology of transfusion reactions.[8,9] It has been suggested that reducing the amount of plasma in platelet units could give fewer transfusion reactions.

Indeed a number of studies have suggested that the use of PAS as storage medium significantly decreases the transfusion reaction rate, especially that of allergic reactions,

after platelet transfusion.[10-14] However, the majority of these studies concern transfusion of apheresis platelets to hematologic patients, so the results of these previous studies may not be applicable to other patients, like trauma or cardiac surgery patients, receiving platelet transfusions. In cardiac surgery patients the cardiopulmonary bypass results in an inflammatory response, endothelial dysfunction and vasoplegia which might influence the occurrence of transfusions reactions.[15,16] Thus, it is unclear whether pooled, buffy-coat-derived platelet units in PAS lead to fewer transfusion reactions compared to platelet units in plasma in the entire population of patients transfused with platelets.

In addition to the possible difference between PAS-platelets and plasma-platelets with regard to safety aspects like transfusion reactions, also the efficacy is of major concern. It is unclear whether PAS-platelet concentrates are as effective as plasma-platelet concentrates. A large in vitro study, comparing platelets in plasma with platelets stored in different PASs for 8 days, demonstrated inferior results for PAS-platelets compared to plasma-platelets, with regard to pH, lactate production, Annexin A5 binding and CD62P expression.[17] However, testing in this study testing was performed in the absence of red blood cells and blood plasma. Furthermore, the correlation between the analyzed in-vitro outcomes 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.[11,18] The results of these hematological studies are not applicable to surgical and trauma patients, in whom considerable volume replacement can occur. In these previous studies the corrected count increment (CCI) is used as a measure for the efficacy of platelet transfusions. While the absolute count increment expresses the absolute increase in platelet count after transfusion, the corrected count increment (CCI) takes the platelet dose and the body surface area of the patient into account. So the CCI only provides information on the platelet count (in a stable blood volume / non-bleeding patient) and does not provide any information on the platelet function of the transfused platelets. It is not clear whether and to what extent CCI is correlated to clinical endpoints such as bleeding and applicable as an adequate surrogate endpoint.[19]

In contrast, multiple electrode aggregometry (Multiplate) is a platelet function test reported to correlate well with clinically relevant outcomes like bleeding and thromboembolic events in different clinical settings.[20-23] The Multiplate is a point-of-care (POC), impedance aggregometer which measures platelet aggregation in whole-blood samples using several agonists. Another clinically frequently used assay that has a clear correlation with clinical endpoints is thromboelastography (TEG) which is a whole-blood POC test assessing overall clot formation.[24,25]

***Storage time***

Besides storage medium also the storage time of platelet concentrates is of interest with regard to safety and efficacy of platelet transfusions. Platelet products are stored for a maximum of 4–7 days, depending on national guidelines and type of product.[26-28] Storage time has been associated with the accumulation of biological response modifiers, such as inflammatory cytokines and chemokines.[29-32] Whether these changes also have clinical consequences is not clear yet, as published results are contradictory. A review paper concluded that the risk of transfusion reactions was similar in old compared to fresh leukoreduced units,[28] whereas a more recent study showed that prolonged storage of platelets was associated with a higher frequency of inflammatory reactions, but not of allergic reactions.[33]

*In vitro* studies show that during storage platelets undergo multiple changes in structure and function collectively known as the "platelet storage lesion".[34,35] In patients this "platelet storage lesion" may result in a reduced hemostatic capacity.[36-38]

## Part II: Platelet transfusions in cardiac surgery patients

***Impact platelet transfusion in cardiac surgery***

A significant part of all platelet transfusions is received by cardiac surgery patients.[39] Cardiac surgery carries a high risk for blood loss and blood transfusion due to invasiveness of the procedures and platelet dysfunction secondary to exposure to cardiopulmonary bypass (CPB), hemodilution and the use of (more and more) potent anti-platelet drugs.[40-43] Significant variation, ranging between 1.4% and 24.7% for isolated CABG, exists in platelet transfusion rates between countries, institutions and physicians.[44-46] This variety indicates inappropriate under- and/or overutilization of platelet transfusion and illustrates the lack of consensus on the indication for a platelet transfusion in certain clinical situations. In part this is explained by the platelet transfusions that are administered outside the (national) guidelines and without documented indication, as shown in an national audit in the UK.[47] Furthermore, the existing guidelines are not specific enough and do not cover several aspects of the clinical situation(s).[47] The American Association of Blood Banks (AABB) guidelines provide limited guidance regarding platelet transfusions in cardiac surgery. The following indications for platelet transfusion are mentioned: life-threatening active bleeding, platelet count less than 50,000/microliter in patients undergoing major surgery, and platelet count less than 10,000/microliter.[48] They caution against prophylactic preoperative transfusion of platelets in most instances, but note that transfusion may be appropriate in instances where there is perioperative bleeding and clinical suspicion for platelet dysfunction. In the 2017

EACTS/EACTA guidelines on platelet transfusions state that platelets should be transfused in bleeding patients with a platelet count below 50,000/microliter or patients on antiplatelet therapy with bleeding complications. (class of recommendation IIa, level of evidence C)[49] However, these guidelines do not provide clarity about several aspects of perioperative bleeding nor do they specify how to determine or confirm platelet dysfunction. This is because evidence regarding these clinical topics is lacking. Unlike for red blood cell transfusions, there are no studies available in which a certain platelet count or platelet function value served as a threshold for platelet transfusion and could be identified as the key effector to stop/reduce perioperative bleeding.[50] Moreover, there is a lack of clinical evidence establishing the hemostatic effect(iveness) of platelet transfusions in cardiac surgery patients.[51]

In addition, conflicting results have been reported regarding the safety of platelet transfusions in the setting of cardiac surgery as some studies have suggested that platelet transfusion may be associated with increased morbidity and mortality, while others have shown no difference with and without platelet transfusion with regard to safety.[52-58] Thus there is an unmet need to determine the clinical impact (safety and efficacy) of perioperative platelet transfusions in patients undergoing cardiac surgery.

***Impact storage time platelets in cardiac surgery patients***

As mentioned before *in vitro* studies show that during storage platelets undergo multiple changes in structure and function collectively known as the "platelet storage lesion".[34,35] It is conceivable that in patients this "platelet storage lesion" results in a reduced hemostatic capacity and more adverse events.[36-38] A recent review showed that transfusion of older platelets was associated with a shorter time to the next transfusion, a trend towards a higher risk of bleeding, and in hematology patients an increased need of platelet transfusions.[28] However, most clinical studies have been performed in non-bleeding hematology patients. Their results may not be applicable to cardiac surgery patients who have different needs (to stop or educe bleeding), different circumstances (like the use of antiplatelet medication and cardiopulmonary bypass) and platelet transfusion may have a different effect.

## Aim and outline of this thesis

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 by studying the influence of one unit of platelets, the influence of storage medium and the influence of storage time on clinical outcomes of patients. Expansion of knowledge about this topic can create possibilities to further improve the safety and efficacy of platelet transfusions.

This thesis starts with the question whether certain aspects of a platelet unit influence its efficacy and safety. It has been suggested that reducing the amount of plasma in platelet units could give fewer 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 the **second chapter** of this thesis we compared patients transfused with PAS-B-platelets, PAS-C-platelets, or plasma-platelets with regard to the occurrence of transfusions reactions in all types of patients transfused with platelets in routine clinical use.

In addition to the possible difference between PAS-platelets and plasma-platelets with regard to safety aspects like transfusion reactions, also the efficacy is of major concern. It is unclear whether PAS-platelet concentrates are as effective as plasma-platelet concentrates. **Chapter three** shows an in-vitro study comparing the hemostatic function of PAS-platelets to plasma-platelets in reconstituted whole blood. The hemostatic function is measured using Multiplate-derived platelet aggregation and TEG-measured overall clot formation.

Besides storage medium also the storage time of platelet concentrates is of interest with regard to safety and efficacy of platelet transfusions. Storage time has been associated with the accumulation of biological response modifiers, such as inflammatory cytokines and chemokines.[29-32]. Whether these changes also have clinical consequences is not clear yet, as published results are contradictory.[28,33] This controversy indicates that a better understanding of the influence of storage time on safety is needed, and will create an opportunity to further improve platelet transfusions. Therefore the study presented in the **fourth chapter** of this thesis assessed whether there is an association between storage time of (leuko-reduced pooled buffy-coat) platelets and transfusion reactions.

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. Since a significant part of 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 effect(iveness) of platelet transfusions in cardiac surgery

patients.[51] In addition, conflicting results have been reported regarding the safety of platelet transfusions in the setting of cardiac surgery.[52-58] So there is an unmet need to determine the clinical impact (safety and efficacy) of perioperative platelet transfusions in patients undergoing cardiac surgery. In the **fifth chapter** we study the efficacy and safety of platelet transfusion by comparing patients who received a platelet transfusion during cardiac surgery with propensity-score-matched patients who did not receive a transfusion.

As mentioned before *in vitro* studies show that during storage platelets undergo multiple changes in structure and function collectively known as the "platelet storage lesion".[34,35] It is concerned that in patients this "platelet storage lesion" results in a reduced hemostatic capacity and more adverse events.[36-38] Subsequently, the question arose whether this "platelet storage lesions" have clinical significant impact. In the **sixth chapter** we present our study analyzing whether platelet storage time is associated with efficacy and safety outcomes in cardiac surgery patients.

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