Platelet transfusions and patient outcomes after cardiac surgery

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PART I

Platelet transfusions in general

CHAPTER 2

2

Transfusion reactions after transfusion of platelets stored in PAS-B, PAS-C or plasma: a nationwide comparison

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Background

Platelets (PLTs) stored in PLT additive solution (PAS) are associated with fewer allergic reactions than plasma-stored PLTs. However, earlier studies could not provide conclusive evidence on febrile reactions, and did not analyze other transfusion reactions separately due to limited sample size. We therefore compared incidences of all transfusion reactions of PAS-B- PLTs, PAS-C- PLTs and plasma- PLTs.

Study design and methods

In this observational study, all transfusion reactions reported to the national hemovigilance office of the Netherlands from 2006 to 2015 were included.

Results

During the study period, a total of 2,407 transfusion reactions after PLT transfusions were reported. In that period 553,267 pooled buffy coat-derived PLT units were issued, of which 83,884 were stored in PAS-B, 45,728 in PAS-C and 423,655 in plasma. Regarding transfusion-related circulatory overload, transfusion-related acute lung injury, and "other reactions" no statistically significant differences were observed between the PLT products. When PAS-B-PLT transfusions were compared to plasma-PLT transfusions, the overall relative risk (RR) of transfusion reactions was 0.99 (95% confidence interval: 0.88;1.11); for allergic and febrile non-hemolytic transfusion reactions (FNHTRs) it was 0.66 (0.55;0.80) and 1.54 (1.27;1.86), respectively. When PAS-C-PLTs were compared to plasma-PLTs, the RR was 0.56 (0.46;0.68) for all transfusion reactions; 0.38 (0.28;0.52) for allergic reactions and 0.82 (0.59;1.13) for FNHTRs. When PAS-C-PLTs were compared to PAS-B-PLTs, for all reactions the RR was 0.56 (0.45;0.70); for allergic reactions 0.58 (0.40;0.82) and for FNHTRs 0.53 (0.37;0.75).

Conclusions

PAS-C-PLTs are associated with fewer transfusion reactions compared to plasma-PLTs and compared to PAS-B-PLTs.

Abstract

Introduction

Platelet (PLT) transfusions are used to provide hemostatic capacity to patients with a decreased number or functionality of PLTs.[1] Besides an improved hemostatic capacity, PLT transfusions can also cause transfusion reactions.[2] All transfusion reactions cause some degree of inconvenience for patients, involve increased costs, and potentially result in (severe) morbidity or death. Therefore, efforts, such as leukoreduction and the use of PLT additive solution (PAS), have been made to reduce the occurrence of transfusion reactions over the past decades.[3]

Previous studies have suggested that cytokines and other substances present in the plasma fraction of PLT units play an important role in the etiology of transfusion reactions.[4,5] It has been suggested that reducing the amount of plasma in PLT units could give fewer transfusion reactions. Washing and concentrating the PLTs are performed to decrease the volume of plasma in PLT units, but these are relatively time-consuming and may adversely affect PLT quality.[6-9] PLT additive solution was developed to replace part of the plasma for storage of PLTs. Earlier studies have suggested that the use of PAS as storage medium significantly decreases the transfusion reaction rate, especially that of allergic reactions, following PLT transfusion.[9-13] However, as the majority of studies analyzed data on apheresis PLT units and were performed in hematologic patients, the results of these studies may not be applicable to all patients receiving PLT transfusions. One study included all types of patients, but in this study only apheresis PLTs in PAS-C were transfused.[10] Thus, it is unclear whether pooled, buffy coat-derived PLT units in PAS-B or PAS-C lead to fewer transfusion reactions in a general patient population compared with PLT units in plasma.

In the Netherlands, PLT concentrates stored in both plasma and PAS are used, based on the geographical location of the hospital. This allowed us to validly compare the PAS-B-PLTs, PAS-C-PLTs and plasma-PLTs in one country with one central blood bank and one hemovigilance organization. The objective of this study was to compare PAS-B-PLTs, PAS-C-PLTs and plasma-PLTs with regard to the occurrence of anaphylactic and other allergic reactions, febrile non-hemolytic reactions (FNHTRs), transfusion-associated circulatory overload (TACO) and transfusion-related acute lung injury (TRALI) in routine clinical use.

Material and methods

This nationwide, observational cohort study evaluated the impact of PLT storage medium (PAS-B, PAS-C and plasma) on transfusion reaction rates in the 10-year period from

2006 to 2015. Anonymized data were obtained from the national hemovigilance organization 'Transfusion and Transplantation Reactions in Patients' (TRIP) and the national Sanquin database (eProgesa, MAKsystems, Paris, France).

PLT products

All PLT products, pre-storage leuko- and plasma-reduced, are produced and stored by the Dutch blood bank Sanquin according to national and international standards. Approximately 90% of PLT concentrates are prepared using five ABO identical and Rh-D compatible buffy coats from whole blood donations. These five buffy coats, each containing 25 mL of plasma, are resuspended either in plasma of one of the five donors (plasma-PLTs) or in PLT additive solution (PAS-PLTs). Two types of PAS were used during the studied period: PAS-B (also known as PAS-2 or T-Sol, Baxter (Nivelles, France), Jan 1, 2006 - Nov 30, 2012) and PAS-C (also known as PAS-III or Intersol, Fenwal, a Fresenius company, La Châtre, France) Dec 1, 2012 - Dec 31, 2015). The remaining 10% of PLT units are collected by apheresis. Apheresis units, as well as hyperconcentrated PLT units were excluded from this analysis, since these are transfused for specific indications, including transfusion reactions that were the study objective of this analysis, which would have introduced bias. The total number of issued units per type of PLT product was obtained from the national Sanquin database (eProgresa).

Hemovigilance system

TRIP is the hemovigilance system in the Netherlands that has been operational since 2003. Participation of a hospital is regarded as the professional standard both in the national transfusion guideline and by the Healthcare Inspectorate. [14] Since 2008, in accordance with European legislation, the reporting of serious reactions to TRIP in parallel to the Healthcare Inspectorate as competent authority has been mandatory. Participation by the hospitals has been over 95% each year from 2006.[15] The definitions of reportable reaction types, severity and imputability are described in the annual TRIP report and website. These are similar to the international definitions developed by the International Haemovigilance Network and the hemovigilance working party of the International Society of Blood Transfusion. [16] In these definitions, FNHTRs and mild FNHTRs are collected separately, with FNHTRs being characterized by a temperature rise of ≥ 2°C and/or rigors, and mild FNHTRs by a temperature rise ≥1 and <2°C without rigors. For the comparison of the PLT products mild FNHTRs were not included, as not all hospitals report the mild FNHTRs. However, the numbers of mild FNHTRs are shown in the tables. The reaction type "other reaction" is a collection of reactions that do not fit in the definition of one of the reaction categories defined by TRIP.

Transfusion reactions are classified according to severity in five categories: [16,17]

- Grade 0: no morbidity
- Grade 1: minor morbidity, not life-threatening
- Grade 2: moderate to serious morbidity, may or may not be life-threatening; or leading to hospitalization or prolongation of illness; or associated with chronic disability or incapacity
- Grade 3: serious morbidity, directly life-threatening
- Grade 4: mortality following a transfusion reaction

The probability that a transfusion was responsible for the transfusion reaction is scored in the following imputability grades: "certain", "probable", "possible", "unlikely" and "excluded". [17]

Statistical analyses

General

The statistical analysis plan was reviewed by the departmental review committee before performing the actual analysis. All transfusion reactions in which a pooled buffy coat-derived PLT unit was involved, and which had been reported to TRIP between January 1, 2006, and December 31, 2015, were evaluated. Reactions with an imputability "unlikely" were included in the overall incidences, but not in the comparisons between the PLT products. In reaction types with fewer than five cases per group the overall incidences were reported, but no comparisons were made between the different PLT products. In addition, the reaction types anaphylactic and other allergic reaction were also evaluated as one category: allergic reactions. (Suspected) bacterial and viral transfusion-transmitted infections were included in the overall numbers, but were not evaluated separately as this information is reported elsewhere.[18]

Comparison of storage media

Only reactions with imputability "certain", "probable" or "possible" were included in the comparisons of transfusion reactions between the products. The transfusion reaction incidences of the three PLT storage media (PAS-B, PAS-C and plasma) were compared using logistic regression-derived odds ratios (ORs) with 95% confidence intervals (CIs). Due to the design of the study these odds ratios can be interpreted as risk ratios (RR).[19] Additionally, a sensitivity analysis was performed to assess whether transfusion of red blood cells (RBCs) or plasma disturb the results of the main analysis. In the sensitivity analysis transfusion reactions were excluded in which a combination of different types of blood products was involved.

Adjustment for potential confounding by centers

In the Netherlands, the type of storage medium of PLT units a hospital is supplied with is determined by the region. In one region hospitals are supplied with PAS-PLTs and in the other regions the hospitals are supplied with plasma-PLTs. In table S2 (available as supporting information in the online version of this paper) an overview can be found of all Dutch hospitals and the PLT product they are supplied with. This distribution of one or other type of PLT products to each of the hospitals may confound our results because the hospital determines both the type of PLT product and the reported transfusion reaction rate. The rate of reported transfusion reactions of hospitals may be influenced by the transfused blood product, but also by the transfusion policy and practice, and the patient population as well as the hospital's reporting instructions and discipline.

By weighting for hospital reporting rate, we reduced the potential confounding impact of the hospitals. As all Dutch hospitals use the same type of RBC units, the incidence of reported transfusion reactions after RBC transfusions was used as a measure for reporting tendency of the hospital. The incidences of non-university hospitals were grouped according to the PLT product they used (plasma-PLTs, PAS-B-PLTs or PAS-C-PLTs) because the number of transfusions per hospital was small. For university hospitals the incidences were calculated separately for every hospital. If a hospital switched to another PLT product separate incidences were calculated for the different periods. All RBC incidences of the hospital (group) were divided by the national RBC incidence to correct for reporting tendency, and then the inverse of this ratio was used as a weight. The transfusion reactions were weighted by these calculated inverses in our analyses. The incidences of transfusion reactions were thus weighted according to the following equation:

$$\textit{weighted incidence per center} = \frac{\textit{unweighted incidence per center}}{\textit{(center RBCs transfusion reaction incidence / national RBCs transfusion reaction incidence)}}$$

Results

General

Between 2006 and 2015, a total of 553,267 pooled buffy coat PLT units were issued in the Netherlands of which 83,884 were stored in PAS-B, 45,728 in PAS-C and 423,655 in plasma. In that period, 2,407 (0.43%) reactions involving PLTs were reported. For each transfusion reaction type, Table 1 shows the number of reported cases and proportion of the total number of transfusion reactions. Additionally, overall incidences for each reaction type are presented. The most frequent reactions were allergic transfusion

Table 1 Incidence of reported transfusion reactions

Reaction type	Number	Incidence (per 10,000)	% of total
Allergic reaction	1,144	21	47.5
• Anaphylactic reaction	262	5	10.9
• Other allergic reaction	882	16	36.6
FNHTR overall	842	15	35.0
• FNHTR	684	12	28.5
• Mild FNHTR	158	3	6.6
TACO	58	1	2.4
TRALI	44	1	1.8
Acute hemolytic reaction	8	0.1	0.3
Delayed hemolytic reaction	4	0.1	0.2
PTP	3	0.1	0.1
(Suspected) infection*	70	1	2.9
Other reaction	234	4	9.7
Overall	2,407	43	100

Data reported are absolute numbers, incidences (per 10,000), calculated by dividing the number of reactions by the total number of PLT units, and the percentage of each reaction type among all reactions.

* (Suspected) transfusion-transmitted bacterial/viral infection

FNHTR non-hemolytic transfusion reaction; PTP post-transfusion purpura; TACO transfusion-associated circulatory overload; TRALI transfusion-related acute lung injury

reactions with an overall incidence of 0.21%, and non-hemolytic transfusion reactions with an overall incidence of 0.15%. A few cases of hemosiderosis and delayed hemolytic reaction were reported, but all these cases were preceded by transfusion of not only PLTs, but also plasma and/or RBC. The majority, 2,085 of 2,407 (86.8%) of the reported reactions were classified as severity grade 1. In total, 268 reactions were associated with serious morbidity (grade 2 or higher), of which 14 had a fatal clinical outcome (grade 4).

Transfusion reactions in PLTs in PAS-B, PAS-C and plasma

The absolute numbers, the incidences and the RRs of the crude unweighted analysis are shown in Table 2, and the RRs resulting from the weighted main analysis are shown in Table 3. When PAS-B-PLTs were compared to plasma-PLTs in the weighted analysis the RR was 0.56 (95%CI 0.37;0.84) for anaphylactic reactions; 0.69 (0.56;0.85) for other allergic reactions and 1.54 (95%CI 1.27;1.86) for FNHTR. When PAS-C-PLTs were compared to plasma-PLTs the RR was 0.27 (95%CI 0.18;0.41) for other allergic reactions, and no difference was demonstrated regarding FNHTRs and anaphylactic reactions. When PAS-C-PLTs were compared to PAS-B-PLTs the RR was 0.53 (95%CI 0.37;0.75) for FNHTRs and 0.39 (95%CI 0.25;0.62) for anaphylactic reactions, but for other allergic reactions no

Table 2 Crude comparison of incidence of transfusion reactions across different storage media

	Number and incidence †						Risk ratio (95%CI) ‡		
PLTs in	PAS-B n=83,884		PAS-C n=45,728		plasma n=423,655		PAS-B vs plasma	PAS-C vs plasma	PAS-C vs PAS-B
Allergic reaction	116	(0.14)	50	(0.11)	978	(0.23)	0.60 (0.49;0.73)	0.47 (0.36;0.63)	0.79 (0.57;1.10)
• Anaphylactic reaction	23	(0.03)	14	(0.03)	225	(0.05)	0.52 (0.34;0.79)	0.58 (0.34;0.99)	1.12 (0.58;2.17)
• Other allergic reaction	93	(0.11)	36	(0.08)	753	(0.18)	0.62 (0.50;0.77)	0.44 (0.32;0.62)	0.71 (0.48;1.04)
FNHTR overall	169	(0.20)	64	(0.14)	609	(0.14)	1.40 (1.18;1.66)	0.97 (0.75;1.26)	0.69 (0.52;0.93)
• FNHTR	130	(0.15)	57	(0.12)	497	(0.12)	1.32 (1.09;1.60)	1.06 (0.81;1.40)	0.80 (0.59;1.10)
• Mild febrile reaction	39	(0.05)	7	(0.02)	112	(0.03)	NR	NR	NR
TACO	11	(0.01)	6	(0.01)	41	(0.01)	1.36 (0.70;2.64)	1.36 (0.58;3.19)	1.00 (0.37;2.71)
TRALI	10	(0.01)	0	(0)	34	(0.008)	1.49 (0.73;3.01)	NR	NR
Acute hemolytic reaction	1	(0.001)	0	(0)	7	(0.002)	NR	NR	NR
Delayed hemolytic reaction	2	(0.002)	0	(0)	2	(0.0005)	NR	NR	NR
PTP	0	(0)	1	(0.002)	2	(0.0005)	NR	NR	NR
(Suspected) infection*	10	(0.01)	4	(0.009)	55	(0.013)	NR	NR	NR
Other reaction	24	(0.03)	19	(0.04)	191	(0.05)	0.64 (0.42;0.97)	0.92 (0.58;1.48)	1.45 (0.80;2.65)
Overall	344	(0.41)	144	(0.31)	1,919	(0.45)	0.90 (0.80;1.01)	0.70 (0.59;0.82)	0.77 (0.64;0.94)

† absolute unweighted numbers and incidences per 100; **‡** risk ratios (95% confidence interval) of the two PAS-PLT types, both compared to plasma-PLTs, and of the PAS-C-PLTs compared to the PAS-B PLTs.

* (Suspected) transfusion-transmitted bacterial/viral infection

CI confidence interval; FNHTR non-hemolytic transfusion reaction; NR not reported; PAS PLT additive solution; PLTs PLTs; PTP post-transfusion purpura; TACO transfusion-associated circulatory overload; TRALI transfusion-related acute lung injury

Table 3 Comparison of transfusion reactions associated with PLTs in PAS-B, PAS-C and plasma, weighted for hospital reporting rates

	Risk ratio (95%CI)		
PLTs in	PAS-B vs plasma	PAS-C vs plasma	PAS-C vs PAS-B
Allergic reaction	0.66 (0.55;0.80)	0.38 (0.28;0.52)	0.58 (0.40;0.82)
• Anaphylactic reaction	0.56 (0.37;0.84)	0.73 (0.44;1.19)	1.32 (0.72;2.43)
• Other allergic reaction	0.69 (0.56;0.85)	0.27 (0.18;0.41)	0.39 (0.25;0.62)
FNHTR	1.54 (1.27;1.86)	0.82 (0.59;1.13)	0.53 (0.37;0.75)
TACO	1.34 (0.69;2.59)	1.59 (0.72;3.52)	1.19 (0.47;3.06)
TRALI	1.08 (0.46;2.50)	NR	NR
Other reaction	0.75 (0.49;1.15)	0.81 (0.47;1.39)	1.07 (0.55;2.08)
Overall	0.99 (0.88;1.11)	0.56 (0.46;0.68)	0.56 (0.45;0.70)

Risk ratios with 95% confidence interval, weighted for reporting rate.
CI confidence interval; FNHTR non-hemolytic transfusion reaction; NR not reported; PAS PLT additive solution; PLTs PLTs; PTP post-transfusion purpura; TACO transfusion-associated circulatory overload; TRALI transfusion-related acute lung injury

difference was demonstrated. Regarding TACO, TRALI and "other reactions" no statistically significant differences were observed between the different PLT products.

Sensitivity analyses

The results of the sensitivity analyses studying reactions where only PLT transfusions were involved are shown in Table S1 (available as supporting information in the online version of this paper). The RRs observed in these analyses for the different reaction types were similar to those found in the main analysis.

Discussion

In this nationwide study, PAS-C-PLTs were associated with a lower overall transfusion reaction incidence than both plasma-PLTs and PAS-B-PLTs. Furthermore, PAS-B-PLTs were associated with a lower incidence of allergic reactions, but had a higher incidence of FNHTR than plasma-PLTs. Regarding TACO, TRALI and "other reactions" no statistically significant difference was observed between the different PLT products.

Our finding that both PAS-B and PAS-C as storage fluid may decrease the risk of allergic reactions compared to plasma is consistent with results of studies on both pooled and apheresis PLTs.[10,11,13] It has been hypothesized that the replacement of most of the plasma, and thereby the amount of allergens in the PLT unit, reduces the risk of allergic

reactions.[20-22] PLT concentrates in PAS still require at least 30% plasma for the PLTs to maintain their quality, likely due to glucose and the buffering capacity of bicarbonate.[23,24] Likely, with the development of glucose- and bicarbonate-containing PASs,[25] the volume of plasma can be reduced further, potentially resulting in fewer allergic reactions. The comparison between PAS-B and PAS-C has not been made before, and our data show that PAS-C-PLTs have a 40% to 50% lower incidence of allergic reactions than PAS-B-PLTs. Although the concentrations of plasma were similar in both PASs, the allergic reaction rates in the PASs differed. This suggests that not only plasma and PLTs, but also the PAS fluid affects the chance of allergic reactions and furthermore that also the type of PAS influences the allergic reaction incidence. Elucidation of the underlying mechanism could benefit further reduction of the allergic reaction rate after PLT transfusions.

The incidence of FNHTRs was increased after transfusion of PAS-B-PLTs compared to plasma-PLTs. This finding is partially in agreement with two previous studies.[13,20] Both earlier studies showed no significant difference between the FNHTR rates of the two PLT products, probably because the patient populations were considerably smaller. However, the study in France did show a trend towards more FNHTRs in the pooled PLTs in PAS.[20] It is assumed that, besides other factors, PLT-derived soluble CD40L can cause FNHTR.[26,27] The release of soluble CD40L is induced by activation of PLTs during preparation and storage.[28,29] Transfusion of plasma-stored PLTs seems to lead to fewer FNHTRs than PAS-B-stored PLTs, which suggests that plasma is more capable of inhibiting PLT activation than PAS-B. When PAS-C-PLTs were compared to plasma-PLTs in our study, no difference was detected, which is consistent with one study but not with the other.[10,11] Furthermore, PAS-C-PLTs were compared to PAS-B-PLTs and demonstrated a lower incidence of FNHTR with the former. No previous literature was found on the clinical comparison of these products. The main difference in the composition of PAS-B and PAS-C is that, in contrast to PAS-B, PAS-C contains phosphate. The advantages of phosphate are that it supplies inorganic phosphate for ATP synthesis and that it functions as a buffer.[30] Possibly these two effects of phosphate in PAS-C explain the difference in FNHTRs between the PAS products. We postulate that better storage characteristics of PLTs in PAS-C, with less soluble CD40L release, are the explanation for our observation, but further in vitro studies need to be conducted.

To the best of our knowledge, this is the first study to directly compare PLTs stored in PAS-B, PAS-C and plasma concerning the less frequent reactions TACO, TRALI and anaphylactic reactions. This study hereby contributes relevant clinical knowledge as these less common reactions comprise more than 15% of all reactions and can lead to severe morbidity and even mortality. For TACO and TRALI, no significant differences were detected between the various PLT products. In contrast, for anaphylactic reactions

PLTs stored in PAS-B demonstrated a significantly lower incidence than PLTs in plasma. However, no significant difference was observed between PAS-C-PLTs and plasma-PLTs, which is remarkable as we expected an effect in the same direction as the PAS-B-PLTs. This may be the result of a lack of statistical power and warrants further study in a larger cohort.

The TRIP data are based on passive surveillance of transfusion reactions. This is both a limitation, because not all reactions are detected and reported, and a strength, because the reactions that are reported to TRIP are probably the most relevant reactions. The overall incidence of reported reactions in our study is relatively high compared to other countries using passive surveillance. As the incidence of transfusion reactions associated with red blood cells is also relatively high in the Netherlands, it is plausible that it reflects the accuracy of the hemovigilance system.[31,32] Another explanation for the relatively high incidence is that some other hemovigilance systems only report serious reactions. The main limitation of this study is that the use of either PAS-PLTs or plasma-PLTs is determined per hospital, so the reporting tendency of hospitals may be a confounder in this study. In order to reduce this confounding, the reactions were weighted, but residual confounding cannot be ruled out. An important strength of our study is that it spans a period of 10 years and is nationwide, which means that it covers all patients who were transfused with pooled buffy coat-derived PLTs. Moreover, our analysis included over half a million PLT transfusions, which made it possible to analyze less common reaction types like anaphylactic reactions, TRALI and TACO separately. Finally, it was possible to compare PLTs in plasma to both PLTs in PAS-B and PAS-C, which provides insights that assist in further improvement of PLT additive solutions. The sensitivity analysis suggests that the results of the main analysis are not affected by blood products other than PLTs.

In conclusion, PAS-C-PLTs appear to induce fewer transfusion reactions compared to plasma-PLTs and PAS-B-PLTs. Furthermore, PAS-B-PLTs are associated with fewer allergic reactions, but with more FNHTR than plasma-PLTs. While PAS has been used as a strategy to mitigate TRALI, our data do not allow any conclusions with respect to TRALI.

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Table S1 Comparison of transfusion reactions of platelets in PAS-B, PAS-C and plasma, weighted for hospital reporting rates (sensitivity analysis*)

		risk ratio (95%CI)	
Platelets in	**PAS-B vs plasma**	**PAS-C vs plasma**	**PAS-C vs PAS-B**
Allergic reaction	0.66 (0.54;0.80)	0.39 (0.28;0.54)	0.59 (0.41;0.85)
• Anaphylactic reaction	0.55 (0.36;0.86)	0.81 (0.50;1.31)	1.46 (0.78;2.71)
• Other allergic reaction	0.69 (0.55;0.85)	0.27 (0.17;0.41)	0.39 (0.24;0.63)
FNHTR	1.55 (1.26;1.90)	0.85 (0.61;1.20)	0.55 (0.38;0.80)
TACO	1.17 (0.47;2.92)	0.29 (0.03;2.84)	0.25 (0.02;2.72)
TRALI	0.30 (0.04;2.12)	NR	NR
Other reaction	0.80 (0.51;1.27)	0.54 (0.26;1.10)	0.67 (0.30;1.52)
Overall	0.97 (0.86;1.10)	0.52 (0.42;0.64)	0.53 (0.42;0.67)

Risk ratios with 95% confidence interval, weighted for reporting rate.

FNHTR non-hemolytic transfusion reaction; NR not reported; PTP post-transfusion purpura; TACO transfusion-associated circulatory overload; TRALI transfusion-related acute lung injury

* In the sensitivity analysis transfusion reactions were excluded when a combination of different types of blood products was involved.

Table S2 The platelet storage medium of the hospitals in the Netherlands

Hospital	Period	Storage medium
Academic Medical Center of Amsterdam	January 2006 - December 2015	plasma
Academic Hospital Maastricht	January 2006 - December 2015	plasma
Admiraal De Ruyter Hospital	January 2006 - December 2015	PAS
Albert Schweitzer Hospital	January 2006 - December 2015	PAS
Amphia Hospital	January 2006 - December 2015	PAS
Amstelland Hospital	January 2006 - December 2015	plasma
Antoni of Leeuwenhoek	January 2006 - December 2015	plasma
Antonius Hospital	January 2006 - December 2015	plasma
Atrium Medical Center Parkstad	January 2006 - December 2015	plasma
Bernhoven Hospital	January 2006 - December 2015	plasma
Bethesda Hospital	January 2006 - December 2015	plasma
Bovenij Hospital	January 2006 - December 2015	plasma
Bronovo Hospital	January 2006 - December 2007	plasma
Bronovo Hospital	January 2008 - December 2015	PAS
Canisius-Wilhelmina Hospital	January 2006 - December 2015	plasma
Catharina Hospital	January 2006 - December 2015	plasma
Christian Hospital Nij Smellinghe	January 2006 - December 2015	plasma
Deventer Hospitals	January 2006 - December 2015	plasma
Diaconessenhuis Leiden	January 2006 - December 2010	plasma
Diaconessenhuis Leiden	January 2011 - December 2015	PAS
Diaconessenhuis Meppel	January 2006 - December 2015	plasma
Diakonessenhuis	January 2006 - December 2015	plasma
Elkerliek Hospital	January 2006 - December 2015	plasma
Erasmus Medical Center	January 2006 - December 2015	PAS
FlevoHospital	January 2006 - December 2015	plasma
Franciscus Hospital	January 2006 - December 2015	PAS
Gelderse Vallei Hospital	January 2006 - December 2015	plasma
Gelre Hospitals	January 2006 - December 2015	plasma
Gemini Hospital	January 2006 - December 2015	plasma
Groene Hart Hospital	January 2006 - December 2015	PAS
Haga Hospital	January 2006 - December 2015	PAS
Haven Hospital	January 2006 - December 2015	PAS
Hofpoort Hospital	January 2006 - December 2015	plasma
Hospital De Tjongerschans	January 2006 - December 2015	plasma
Hospital Group Twente	January 2006 - December 2015	plasma
IJsselland Hospital	January 2006 - December 2015	PAS
Ikazia Hospital	January 2006 - December 2015	PAS
Isala Hospital	January 2006 - December 2015	plasma

Table S2 continued

Hospital	Period	Storage medium
Jeroen Bosch Hospital	January 2006 - December 2015	plasma
Kennemer Gasthuis	January 2006 - February 2009	plasma
Koningin Beatrix Hospital	January 2006 - December 2015	plasma
Laurentius Hospital	January 2006 - December 2015	plasma
Leiden University Medical Center	January 2006 - July 2014	plasma
Leiden University Medical Center	July 2014 - December 2015	PAS
Lievensberg Hospital	January 2006 - December 2015	PAS
Maasstad Hospital	January 2006 - December 2015	PAS
Maasstad Hospital	January 2006 - December 2015	PAS
Martini Hospital	January 2006 - December 2015	plasma
Máxima Medical Center	January 2006 - December 2015	plasma
Meander Medical Center Amersfoort	January 2006 - December 2015	plasma
Medial	January 2006 - December 2015	plasma
Medical Center Alkmaar	January 2006 - December 2015	plasma
Medical Center Haaglanden	January 2006 - December 2015	PAS
Medical Center Leeuwarden	January 2006 - December 2015	plasma
Medical Spectrum Twente	January 2006 - December 2015	plasma
Ommelander Hospital Group	January 2006 - December 2015	plasma
Onze Lieve Vrouwe Gasthuis	January 2006 - December 2015	plasma
Orbis Medical Center	January 2006 - December 2015	plasma
Radboud University Medical Center	January 2006 - December 2015	plasma
Refaja Hospital	January 2006 - December 2015	plasma
Reinier de Graaf Groep	January 2006 - December 2015	PAS
Rijnland Hospital	January 2006 - September 2008	plasma
Rijnland Hospital	September 2008 - December 2015	PAS
Rijnstate Hospital	January 2006 - December 2015	plasma
Rivas Zorggroep	January 2006 - December 2015	PAS
Rivierenland Hospital	January 2006 - December 2015	plasma
Rode Kruis Hospital	January 2006 - December 2015	plasma
Saxenburgh Groep	January 2006 - December 2015	plasma
Scheper Hospital	January 2006 - December 2015	plasma
Slingeland Hospital	January 2006 - December 2015	plasma
Slotervaart Hospital	January 2006 - December 2015	plasma
Spaarne Hospital	January 2006 - December 2015	plasma
Spijkenisse Medical Center	January 2006 - December 2015	PAS
St. Anna Hospital	January 2006 - December 2015	plasma
St. Antonius Hospital	January 2006 - December 2015	plasma
St. Antonius Hospital	January 2006 - December 2015	plasma
St. Elisabeth Hospital	January 2006 - December 2015	plasma

Table S2 continued

Hospital	Period	Storage medium
St. Franciscus Gasthuis	January 2006 - December 2015	PAS
St. Jansdal Hospital	January 2006 - December 2015	plasma
St. Lucas Andreas Hospital	January 2006 - December 2015	plasma
St. Maartenskliniek	January 2006 - December 2015	plasma
Synergos St. Jans Gasthuis	January 2006 - December 2015	plasma
t Lange Land Hospital	January 2006 - February 2009	plasma
t Lange Land Hospital	February 2009 - December 2015	PAS
Tergooi Hospitals	January 2006 - December 2015	plasma
Tweesteden Hospital	January 2006 - December 2015	plasma
University Medical Center Groningen	January 2006 - December 2015	plasma
University Medical Center Utrecht	January 2006 - December 2015	plasma
Van Weel Bethesda Hospital	January 2006 - December 2015	PAS
VieCuri Medical Center Noord-Limburg	January 2006 - December 2015	plasma
Vlietland Hospital	January 2006 - December 2015	PAS
VU Medical Center	January 2006 - December 2015	plasma
Waterland Hospital	January 2006 - December 2015	plasma
Westfriesgasthuis	January 2006 - December 2015	plasma
Wilhelmina Hospital Assen	January 2006 - December 2015	plasma
Zaans Medical Center	January 2006 - December 2015	plasma
Zorgsaam Zeeuws-Vlaanderen	January 2006 - December 2015	PAS