The bright and the dark side of blood transfusion : turning data into knowledge

Caram Deelder, C.; Caram Deelder C.

CHAPTER 3

Age of platelet concentrates and time to the next transfusion

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Camila Caram-Deelder[1;2]; Johanna G. van der Bom[1;2]; Hein Putter[3]; Anja Leyte[4]; Daan van de Kerkhof[5]; Dorothea Evers[1;6]; Erik A. Beckers[7]; Floor Weerkamp[8]; Francisca Hudig[9]; Jaap Jan Zwaginga[1;6]; Jan M. M. Rondeel[10]; Karen M. K. de Vooght[11]; Nathalie C. V. Péquériaux[12]; Otto Visser[13]; Jonathan P. Wallis[14]; Rutger A. Middelburg[1,2].

1. Center for Clinical Transfusion Research, Sanquin Research; 2. Department of Clinical Epidemiology, Leiden University Medical Center; 3. Department of Medical Statistics, Leiden University Medical Center; 4. Departments of Hematology and Clinical Chemistry, Onze Lieve Vrouwe Gasthuis; 5. Department of Clinical Chemistry and Hematology, Catharina Hospital; 6. Department of Immunohaematology and Blood Transfusion, Leiden University Medical Centre; 7. Department of Internal Medicine-Hematology, Maastricht University Medical Center; 8. Department of Clinical Chemistry, Maasstad Ziekenhuis; 9. LabWest, Haga Teaching Hospital; 10. Department of Clinical Chemistry, Isala Zwolle; 11. Department of Clinical Chemistry and Hematology, University Medical Center Utrecht;12. Department of Clinical Chemistry and Hematology, Jeroen Bosch Hospital; 13. Department of Hematology, VU Medical Center; 14. Department of Hematology, Newcastle upon Tyne Hospitals NHS Foundation Trust.

ABSTRACT

Background: Storage time of platelets concentrates has been negatively associated with clinical efficacy outcomes. The aim of this study was, to quantify the association between storage time of platelet concentrates and interval to the next platelet transfusion for different types of platelet components, stored for up to seven days and transfused to transfusion dependent thrombocytopenic hemato-oncology patients.

Methods: From a cohort of patients from 10 major Dutch hospitals, patients were selected whose transfusion patterns were compatible with platelet transfusion dependency due to hemato-oncological disease . Mean time to the next transfusion and mean differences in time to the next transfusion for different storage time categories (i.e. fresh: <4 days, intermediate: 4-5 days, and old: >5 days) were estimated, per component type, using multilevel mixed-effects linear models.

Results: Among a cohort of 29,761 patients who received 140,896 platelet transfusions we selected 4,441 hemato-oncology patients who had received 12,724 platelet transfusions during periods of platelet transfusion dependency. Transfusion of fresh, compared to old, buffy coat-derived platelets in plasma was associated with a delay to the next transfusion of 6.2 hours(95% confidence interval (CI): 4.5 to 8.0). For buffy coat-derived platelets in PAS-B and C this difference was 7.7 hours (CI:2.2 to 13.3) and 3.9 hours (CI:-2.1 to 9.9) while for apheresis platelets in plasma it was only 1.8 hours (CI: -3.5 to 7.1).

Conclusion: Our results indicate that the time to the next transfusion shortens with increasing age of transfused buffy coat-derived platelet concentrates. This association was not observed for apheresis platelets.

INTRODUCTION

The majority of platelet transfusions are given prophylactically to prevent bleeding in hemato-oncological patients who have become thrombocytopenic as a result of disease-related or treatment-induced severe bone marrow suppression.[1] Prophylactic transfusions are routinely prescribed in case of reversible bone marrow failure, while patients have negligible endogenous platelet production, whenever platelet counts drop below $10x10^9$ platelets/L.[2] In this situation, where the indication for the next transfusion depends only on the platelet count, a lower platelet count increment or reduced platelet survival after platelet transfusion will result in a shorter interval to the next transfusion. Consequently a higher cumulative number of transfusions could be needed with all associated risks and costs.

Several studies have reported associations between storage time of platelet concentrates and outcomes. Recently two published meta-analyses showed that storage time plays an important role in the balance between efficacy, safety, and costs.[3,4] Time to the next transfusion, as an outcome, was found to be reported in eight reviewed papers.[5-12] Four of these studies could be meta-analyzed and estimated the interval between platelet transfusions after transfusion of old platelets to be 0.25 days (CI: 0.13 to 0.38) shorter as compared to transfusion of fresh platelets.[3,5-8]

The influence of storage time on platelet recovery and survival could be affected by the type of platelet component transfused. Different production methods and storage solutions may lead to differences in the stability of stored platelets. In addition, while most previous studies reported storage times up to 5 days only, in the Netherlands platelets stored in plasma or in platelet additive solution (PAS) C can be stored for up to seven days.

The aim of this study was, to quantify the association between storage time of platelet concentrates and interval to the next platelet transfusion for different types of platelet components, stored for up to seven days and transfused to transfusion dependent thrombocytopenic hemato-oncology patients.

METHODS

Study design and population

Platelet transfusion data from two nationwide databases specifically developed to study blood transfusions were merged. As previously described in more detail, these databases included: (i) consecutive transfused patients who received their first ever blood component transfusion between May 2005 and September 2015 in one of the six participating centers of the case cohort study "Risk Factors for Alloimmunisation after red blood Cell Transfusions (R-FACT)",[13,14] and (ii) patients who were transfused between November 2009 and January 2016 in one of the seven participating centers of the Dutch Transfusion Data warehouse (DTD) project.[15] Information on individual components was provided by the national Dutch blood supply (Sanquin bloedbank) and linked to hospital data using the components identification codes. Figure 1 shows the dataflow through the analyses.

The two databases contain similar information about patients and transfusions. The DTD database has additional information about patients' admissions and diagnoses registered via the DBC system.[16] The DBC system is a

Diagnosis Related Group like system for the registration and reimbursement of treatments provided by medical specialists and hospitals. Table 1s (online supplemental material) provides a list of hematological DBC codes and their descriptions.

Patient selection

For the current analyses we wanted to use the interval between consecutive platelet transfusions as a proxy for platelet recovery and survival after transfusion. This proxy will only give a valid estimate of the influence of storage time (i.e. independent of patient characteristics) if we select only patients for whom: 1. platelet transfusions were given at set platelet count triggers, 2. recovery and survival were not negatively affected by the clinical condition or refractoriness of the patient, and 3. patients had sufficiently suppressed bone marrow activity to make endogenous platelet production negligible.

An algorithm was therefore developed aiming to select platelet transfusions given to severely thrombocytopenic, thrombocyte transfusion dependent patients, who had received dose-intensive myelo-suppressive therapy and neither produced endogenous platelets nor had an accelerated platelet consumption. Based on clinical experience with this patient group we set up the following selection criteria.

From the first of these transfusions onwards the algorithm selected every platelet transfusion given within six days of the previous transfusion, as long as the interval between the two platelet transfusions was at least two days (i.e. 48 hours, not consecutive days). Platelet transfusions given within an interval of two days (i.e. the same or the next day) were excluded because they are likely to be the result of an unsuccessful platelet transfusion, or patients with increased consumption, or bleeding, that may not have had any correlation to the storage time of the platelet component. Consecutive transfusions after seven days or more were excluded because i) at exactly seven days they likely represent a pre-determined weekly protocol irrespective of platelet counts (e.g. during weekly outpatient clinic visits); and ii) transfusions intervals bigger than seven days there is likely some endogenous production of platelets, as transfused platelets are unlikely to survive that long in the circulation.

Patients could be included in multiple distinct periods of transfusion dependency if the platelet transfusion free interval between these periods was at least 14 days. For examples of patient selection and definitions of transfusion periods, see supplemental material.

Validation of the patient selection

It was pre-defined that the algorithm would be considered optimal if all selected patients were eligible, even if not all eligible patients were selected. Therefore, priority was given to specificity (i.e. no ineligible patients included) for three reasons: 1. not all patients with an appropriate DBC code are actually eligible for this study, since they could also be clinically unstable, refractory to platelet transfusions, or not being exposed to myelo-suppresive agents (i.e. we expect a maximum sensitivity achievable of about 75%);[17-19] 2. we do not expect any bias if we exclude some of the eligible patients; 3. conversely, inclusion of ineligible patients is expected to dilute the influence of storage time on time to the next platelet transfusion, since patient-related factors will then be more important.

Validation was carried out in the DTD database only, since the R-FACT database didn't contain information on diagnoses. However, since this meant diagnoses were missing for logistical reasons (i.e. which hospital transfused a patient, and in which database did this hospital participate), missingness of diagnoses was considered to be missing completely at random.[20] Therefore, no difference in validity of the selection is expected between the two databases and a valid algorithm for one database can validly be applied to the other.

The exclusion of transfusions after an interval of seven or more days was aimed at excluding both patients with endogenous platelet production and out-patients. Similar to the diagnosis we could only validate the exclusion of out-patients for the DTD database.

Although we could not directly validate the selection for the absence accelerated platelet consumption, our selection criteria already select for this (i.e. patients with accelerated consumption are expected to need transfusions with intervals of less than two days). Therefore, an additional check was unnecessary.

Furthermore, the results were stratified by hospital and patient's age categories to provide insight into the consistency of the algorithm's performance across levels of these variables.

Blood components

Platelets components in the Netherlands are obtained from apheresis or whole blood donations. Whole blood donations are separated into components and the buffy-coats of five donations with preferable identical (always compatible) ABO and Rh D blood group are pooled and stored in plasma or platelet addictive solution (PAS). In the Netherlands, and consequently in our cohort, PAS-B was used until December 2012 and PAS-C from January 2013 onwards.[21,22] Platelets stored in PAS-B had a maximum shelf-life of five days, platelets stored in PAS-C or plasma have a maximum shelf-life of seven days. Further, platelets in plasma can be hyperconcentrated (i.e. plasma removed), by indication, before being transfused. Hyperconcentration is only applied to components stored for five days or less.[23]

Single donor apheresis platelets are drawn by use of apheresis machines and stored in plasma for up to seven days. In the Netherlands the indications for apheresis platelets are the need to transfuse HLA or HPA typed platelets, neonates and adults in special situations (i.e. ABO incompatibility, volume overload, or allergic reactions).[23]

In short, the components analyzed in this paper were (1) apheresis platelets in plasma, (2) apheresis platelets in plasma - hyperconcentrated (3) buffy coat-derived platelets in PAS-B, (4) buffy coat-derived platelets in PAS-C, (5) buffy coat-derived platelets in plasma, and (6) buffycoat-derived platelets in plasma - hyperconcentrated. Patients who received rarely prescribed components (i.e. apheresis platelets in PAS) or who had incorrect or missing data for any of their platelet transfusions were excluded. Storage times were calculated setting the components' donation date as day 0.

Analyses

Relation between storage time and time to next transfusion

Multilevel mixed-effects linear regression models were used. The modes had three nested levels to account for differences between hospitals (i.e. transfusion protocols), multiple transfusion periods per patient, and repeated measurements

within a single transfusion period (e.g. two intervals, in case of three platelet transfusions during one transfusion period). Our outcome of interest was the time to the next platelet transfusion. The determinant of interest was storage time of transfused platelet concentrates. Models were adjusted for confounding variables (day of the week, patient age and sex and blood group compatibility). All variables were included in the model as discrete (i.e. indicators). Compatibility was included in the model as two independent categorical variables: ABO compatibility (identical, minor, major and bidirectional mismatch) and Rh D compatibility (identical, minor and major mismatch). Both variables also included the category "unknown" to indicate when the patient's blood type was unknown. Blood groups of components were all known. The type of blood component (i.e. production method, additional processing and storage solution) was considered a potential effect modifier and therefore not included as a cofounder in the model. Instead results were stratified by component type.

Each platelet transfusion was classified according to the components' storage time on the day of transfusion: '*fresh'* if the transfused component was up to 3 days old, '*intermediate*' if the component was 4 or 5 days old, and '*old*' if the component was 6 or 7 days old.

Predicted means (also known as marginal means, predicted marginal means and predicted marginal distribution) of the time to the next platelet transfusion were derived from the multilevel models to estimate the average predicted outcome and 95% confidence interval for each storage time category.

Sensitivity and exploratory analyses

Several sensitivity analyses were performed to check the robustness of the results. The first one was the "single storage age" analyses as effects of different levels of exposure (in this study mixed storage age) could potentially carry-over across consecutive platelet transfusions. In other words, a poor outcome for the current platelet transfusion could also be the result of the storage age of the previous platelet transfusion.[24,25] To overcome this potential problem, transfusion periods were classified according to their components' storage time: 'only fresh' platelet transfusions if all the transfused components were up to 3 days old, 'only intermediate' platelet transfusions if all their components were 4 or 5 days old and finally 'only old' if all their components were transfused after 6 or 7 days of storage. "Mixed age" were transfusion periods that mix more than one storage time group. Consequently, in the single storage age analyses mixed age transfusion periods were excluded. The second sensitivity analysis was performed by excluding transfusion periods which contained potential outpatient clinic platelet transfusions (i.e. admission and discharge of patients were on the same day) from the analyses. The aim of this exclusion was to rule out that the transfusions in these patients bias the results because the transfusion indication may not be entirely platelet count dependent.

Third, to verify the algorithm performance regarding to diagnoses selection a sensitivity an analysis including only patients with hematological diagnoses was performed.

To further explore possible confounding and effect modification all models were also stratified by storage time in days, patients' sex, and patients' age (dichotomized as <18 years or ≥18 years).

RESULTS

Source population

The two databases (R-fact study and DTD) combined and cleaned included 29,761 patients who received 140,896 platelet transfusions between March 2004 and January 2016 (figure 1). The majority of patients were male (18,260, 61%) and adult (25,502, 86%). They received a median of two platelet transfusions (interquartile range (IQR) 1 to 3). Twenty-one percent (3,638) of the 16,927 patients with diagnoses available had one or more hematological diseases: 1,472 (9%) leukemia, 845 (5%) lymphoma, 663 (4%) myeloma, and 374 (2%) "other hematological diseases". These patients received 47,704 (59%) of all transfusions (Table 1 - *"full cohort"*). Diagnoses were not available to 12,834 patients, 96% of them (12,281) due to lack of information in the source database (R-fact). Only 553 (2%) patients did not have diagnoses available due to missingness. A total of 140,896 platelets units were transfused: 108,823 (77%) buffy coat-derived platelets in plasma, 17,327 (12%) apheresis platelets in plasma, and 14,746 (10%) buffy coat-derived platelets in PAS. ABO and Rh D identical components corresponded to 67% (94,577) and 73% (102,870) of the transfusions. Components were stored on average for 4.0 days (median 4, IQR (3 to 6)). Of all transfused platelets 45,241 (32%) were fresh (<4 days), 57,549 (41%) were of intermediate age (4-5 days) and 38,101 (27%) were old (>5 days). (Table 1 - *'full cohort'*)

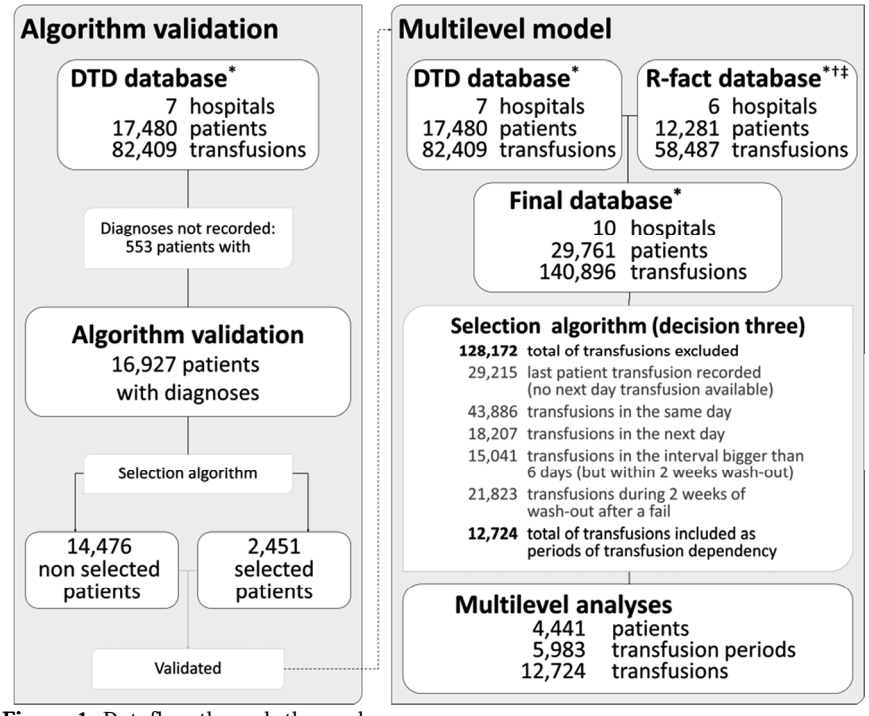

Figure 1: Dataflow through the analyses
DTD: Dutch Transfusion Data warehouse
R-fact: case cohort study "Risk Factors for Alloimmunisation after red blood Cell Transfusions (R-FACT)*Merged to blood supplier database and cleaned: excludes patients who received rarely prescribed products (total of 69 patients) or who had incorrect or missing data (total of 844 patients) †R-fact database does not have diagnoses code. Numbers refer to additional transfusions/patients. Except by hospitals: 6 hospitals in total, 3 new hospitals and 3 hospitals also included in the DTD database‡ three hospitals were common in the DTD and R-fact databases (different follow-up), data duplication was checked by the unique product code

Performance of selection algorithm

Of the 29,761 patients who received platelet transfusions 16,927 had diagnoses available in the source database (i.e. the DTD database), and could be included in the validation of the algorithm (figure 1). 3,638 patients had at least one documented hematological diagnosis and 13,289 did not. Of the 13,289 patients without documented hematological diagnosis 747 were selected by the algorithm while 12,542 were correctly not selected by the algorithm. Thus, the algorithm's overall specificity was 94%. In other words, the probability of not being selected given that the patient does not have any hematological diagnosis was: 12,542/13,289=0.94. From the 3,638 patients with documented hematological diagnoses the algorithm selected 1,704 in one or more periods of transfusion dependency (sensitivity 47%). For children (age <18 years) specificity was 85%, while for adults (≥18 years) specificity was 96%. The algorithm performed similarly for all hospitals (Table 2).

Selected population

Once the algorithm was validated it was applied to the full database. The final selection according to the validated algorithm included 4,441 patients who received 12,724 platelet transfusions in 5,983 transfusion periods (figure 1, table 1). Selected patients received an average of 3.0 transfusions (median 2, IQR: 1 to 3) per transfusion period. 80% of selected patients were adults (median age 56 years, IQR 35 to 65) and 60% male. 1,990 selected patients didn't have diagnoses available. Seventy percent of the 2,451 selected patients, with diagnoses available in the database, had one or more diagnoses of hematological disease. Diagnoses were not available to 1,990 patients, 97% of them (1,940) due to lack of information in the source database (R-fact). Only 50 (1%) patients did not have diagnoses available due to missingness. Leukemia and lymphoma were the most common diagnoses of the selected population (34% and 15%). 78% (9,967) of the transfusions were buffy coat-derived platelets in plasma, 11% (1,442) apheresis platelets in plasma and 10% (1,315) buffy coat-derived platelets in PAS. ABO and Rh D identical components corresponded to 69% (8,733) and 73% (9,334) of the transfusions. 3,649 (29%) of the platelets units were transfused fresh, 5,438 (43%) were transfused at intermedium storage time and 3,637 (29%) units were transfused old. (Table 1 – 'selected cohort')

Table 2: Algorithm performance by patient's age and hospitals

	n	Specificity	Sensitivity
All ages			
All hospitals	16,927	94%	47%
Hospital A	1,505	96%	47%
Hospital B	2,290	96%	47%
Hospital C	4,522	92%	50%
Hospital D	2,201	95%	44%
Hospital E	815	92%	28%
Hospital F	1,868	98%	41%
Hospital G	3,726	93%	51%
Age <18			
All hospitals	2,196	85%	56%
Hospital A	12	NA*	NA*
Hospital B	88	NA*	NA*
Hospital C	877	83%	59%
Hospital D	140	83%	47%
Hospital E	28	NA*	NA*
Hospital F	4	NA*	NA*
Hospital G	1,047	87%	61%
Age ≥18			
All hospitals	14,731	96%	46%
Hospital A	1,493	96%	48%
Hospital B	2,202	97%	48%
Hospital C	3,645	95%	48%
Hospital D	2,061	96%	44%
Hospital E	787	93%	29%
Hospital F	1,864	98%	41%
Hospital G	2,679	96%	48%

*NA: Not available due to the small number of patients

Time to the next transfusion

Figure 2 and table 3 show the time to the next transfusion (in days) for each component and the difference (in hours) between storage time categories. Fresh buffy coat-derived platelets in plasma (<4 days) resulted in a time to the next transfusion of 3.5 days (95% confidence interval (CI): 3.4 to 3.6). Fresh hyperconcentrated buffy coat-derived platelets in plasma resulted in a time to the next transfusion of 3.5 days (CI: 3.3 to 3.6). Fresh buffy coat-derived platelets stored in PAS-C had a time to the next transfusion of 3.1 days (CI: 2.9 to 3.3). Fresh buffy coat-derived platelets stored in PAS-B resulted in a time to the next transfusion of 3.5 days (CI: 3.3 to 3.6). And fresh apheresis platelets in plasma resulted in a time to the next transfusion of 3.3 days (CI: 3.1 to 3.4).

Storage time and time to the next transfusion

Relative to fresh components (<4 days), intermediately stored (4 or 5 days of storage) components had a 3.5 hour shorter (CI: 1.8 to 5.2) interval for buffy coat-derived platelets in plasma, 3.7 hour shorter (CI: -0.6 to 8.0) for hyperconcentrated buffy coat-derived platelets in plasma, 0.1 hour shorter (CI: -5.5 to 5.7) for buffy coat-derived platelets in PAS-C, 7.7 hour shorter (2.2 to 13.3) for buffy coat-derived platelets in PAS-B, 4.7 hour shorter (CI: -0.1 to 9.5) for apheresis platelets in plasma and 0.0 hour longer (CI: -5.6 to -5.7) for hyperconcentrated apheresis platelets in plasma.

Again, relative to fresh components, old components (>5 days) had a 6.2 hours shorter (CI: 4.5 to 8.0) interval for buffy coat-derived platelets in plasma, 3.9 hour shorter (IC: -2.1 to 9.9) for buffy coat-derived platelets in PAS-C, and 1.8 hours shorter (-3.5 to 7.1) for apheresis platelets in plasma.

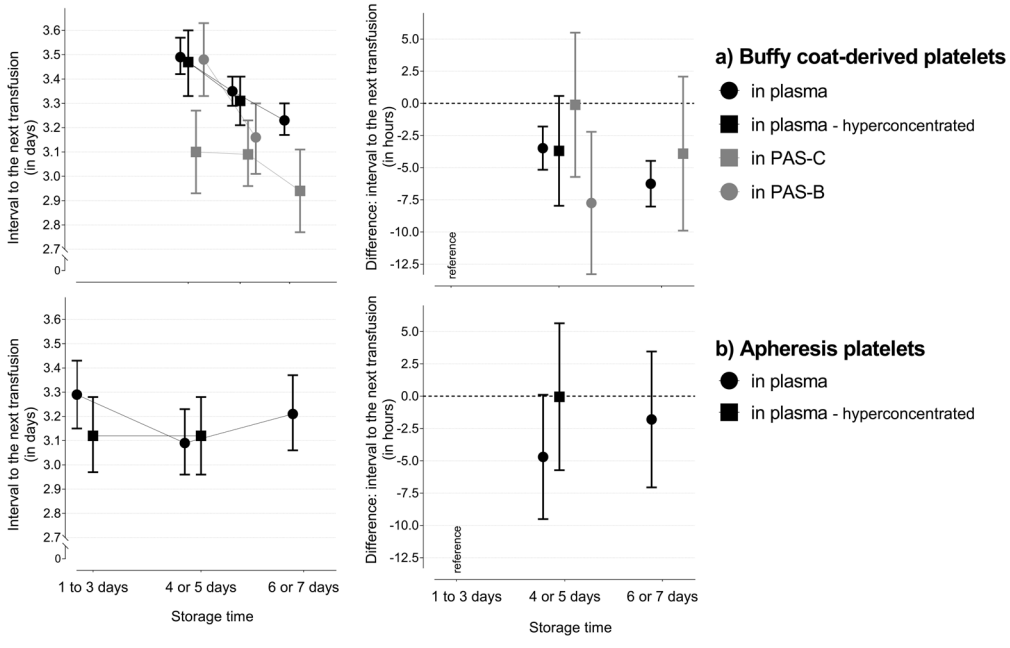

Figure 2 - Interval to the next transfusions (in days) per blood component and difference (in hours)

Table 1: Patient and transfusion characteristics

	Full cohort		Selected cohort	
Patients				
Number of unique patients	29,761		4,441	15%
Transfusion periods	NA		5,983	NA
Female patients	11,062	37%	1,744	39%
Male patients	18,260	61%	2,659	60%
Unknown sex	439	1%	38	1%
Age of patients (in years)*	62	(44-72)	56	(33-65)
<18 years old	4,259	14%	887	20%
≥18 years old	25,502	86%	3,554	80%
Diagnoses per patient				
Not available	12,834	43%	1,990	45%
Not available due to database (R-fact)	12,281	41%	1,940	44%
Not available due to missingness (DTD data)	553	2%	50	1%
Available	16,927	57%	2,451	55%
Others than hematological diseases	13,289	79%	747	30%
Hematological diseases	3,638	21%	1,704	70%
Leukemia†	1,472	9%	844	34%
Chronic leukemia †	238	1%	95	4%
Myeloma†	663	4%	199	8%
Lymphoma†	845	5%	357	15%
Childhood hematological diseases†	204	1%	112	5%
Others hematological diseases†	374	2%	173	7%
Transfusions per patient*	2	(1-3)	2	(1-3)
Transfusions				
Total number of platelets units transfused	140,896		12,724	9%
Buffy coat-derived in plasma	88,802	63%	8,709	68%
Buffy coat-derived in plasma - hyperconcentrated	20,021	14%	1,258	10%
Buffy coat-derived in PAS-C	8,323	6%	625	5%
Buffy coat-derived in PAS-B	6,423	5%	690	5%
Apheresis platelets in plasma	10,966	8%	964	8%
Apheresis platelets in plasma - hyperconcentrated	6,361	5%	478	4%
ABO compatibility‡				
Identical	94,577	67%	8,733	69%
Minor	31,121	22%	2,525	20%
Major	8,249	6%	652	5%
Bidirectional	1,988	1%	154	1%
Unknown	4,961	4%	660	5%
Rh D compatibility‡				
Identical	102,870	73%	9,334	73%
Minor	28,188	20%	2,370	19%
Major	5,581	4%	425	3%
Unknown	4,257	3%	595	5%
Storage time				
1 day	1,999	1%	153	1%
2 days	16,848	12%	1,308	10%
3 days	26,399	19%	2,188	17%
4 days	27,846	20%	2,670	21%
5 days	29,703	21%	2,768	22%
6 days	19,120	14%	1,863	15%
7 days	18,981	13%	1,774	14%
Transfusions per diagnoses				
Not available	59,509	42%	5,747	45%
Not available due to database (R-fact)	58,487	42%	5,677	45%
Not available due to missingness (DTD data)	1,022	1%	70	1%
Available	81,387	58%	6,977	55%
Others than hematological diseases	33,683	41%	1,208	17%
Hematological diseases	47,704	59%	5,769	83%
Leukemia†	24,688	30%	3,594	52%
Chronic leukemia†	3,873	5%	319	5%
Myeloma†	3,696	5%	392	6%
Lymphoma†	5,978	7%	887	13%
Childhood hematological diseases†	3,285	4%	335	5%
Others hematological diseases†	8,710	11%	591	8%

Numbers represent numbers of absolute numbers and percentages unless otherwise indicated.
* median and interquartile range; † multiple answers, percentages of patients with diagnoses available in the database; ‡ Minor compatibility: transfused blood contains antibodies against recipients antigens; Major compatibility: recipients contains antibody against antigens in transfused blood; Bidirectional compatibility: major and minor compatibility combined; Unknown compatibility: patient blood type unknown (blood group of components were all known).

Table 3: Crude and adjusted marginal means and differences of interval to the next transfusions per type of blood component

	Crude			Multilevel (hospital, patient and cycles) adjusted for confounders (weekday, patient age, patient sex, ABO and Rh compatibility)		
	n	Transfusion interval (95% CI) - in days	difference (95% CI) - in hours	n	Transfusion interval (95% CI) - in days	difference (95% CI) - in hours
Buffy coat-derived platelets in plasma						
1 to 3 days	2,099	3.6 (3.5 to 3.6)	reference	2,099	3.5 (3.4 to 3.6)	reference
4 or 5 days	3,435	3.3 (3.3 to 3.3)	-6.8 (-8.3 to -5.2)	3,435	3.3 (3.3 to 3.4)	-3.5 (-5.2 to -1.8)
6 or 7 days	3,175	3.2 (3.2 to 3.3)	-8.9 (-10.5 to -7.3)	3,175	3.2 (3.2 to 3.3)	-6.2 (-8.0 to -4.5)
Buffy coat-derived platelets in plasma - hyperconcentrated						
1 to 3 days	481	3.6 (3.5 to 3.7)	reference	481	3.5 (3.3 to 3.6)	reference
4 or 5 days	777	3.2 (3.1 to 3.3)	-10.3 (-13.7 to -7.0)	777	3.3 (3.2 to 3.4)	-3.7 (-8.0 to 0.6)
6 or 7 days	0	NA	NA	0	NA	NA
Buffy coat-derived platelets in PAS-C						
1 to 3 days	171	3.3 (3.1 to 3.4)	reference	171	3.1 (2.9 to 3.3)	reference
4 or 5 days	276	3.0 (2.9 to 3.2)	-5.6 (-10.8 to -0.4)	276	3.1 (3.0 to 3.2)	-0.1 (-5.7 to 5.5)
6 or 7 days	178	2.9 (2.7 to 3.1)	-8.2 (-13.9 to -2.5)	178	2.9 (2.8 to 3.1)	-3.9 (-9.9 to 2.1)
Buffy coat-derived platelets in PAS-B						
1 to 3 days	338	3.5 (3.3 to 3.6)	reference	338	3.5 (3.3 to 3.6)	reference
4 or 5 days	352	3.1 (3.0 to 3.2)	-8.8 (-13.2 to -4.5)	352	3.2 (3.0 to 3.3)	-7.7 (-13.3 to -2.2)
6 or 7 days	0	NA	NA	0	NA	NA
Apheresis platelets in plasma						
1 to 3 days	321	3.3 (3.1 to 3.4)	reference	321	3.3 (3.1 to 3.4)	reference
4 or 5 days	359	3.0 (2.9 to 3.1)	-6.2 (-10.6 to -1.9)	359	3.1 (3.0 to 3.2)	-4.7 (-9.5 to 0.1)
6 or 7 days	284	3.3 (3.2 to 3.5)	2.0 (-2.6 to 6.6)	284	3.2 (3.1 to 3.4)	-1.8 (-7.1 to 3.5)
Apheresis platelets in plasma - hyperconcentrated						
1 to 3 days	239	3.2 (3.0 to 3.4)	reference	239	3.1 (3.0 to 3.3)	reference
4 or 5 days	239	3.0 (2.9 to 3.2)	-3.6 (-8.9 to 1.6)	239	3.1 (3.0 to 3.3)	0.0 (-5.7 to 5.6)
6 or 7 days	0	NA	NA	0	NA	NA

On average, patients were platelet transfusion dependent for 11.1 days and received platelet transfusions every 3.35 days during that period (total 3.32 platelet transfusions over 11.1 days). When receiving only fresh platelet units, the interval between transfusions would be 3.50 days therefore resulting in a total of 3.17 transfusions compared to an interval of 3.24 days and a total of 3.43 transfusions when receiving only old components. The difference between only fresh and only old would therefore be 0.25 transfusions on average, suggesting that up to one transfusion might be saved on average per 4 patients' admissions or 7% of the patients' transfusions (table 4). Table 4 shows the projected differences for all platelets components.

Sensitivity and exploratory analyses

Results of the different exploratory stratifications and the sensitivity analyses of single storage age, and the analyses after excluding patients without diagnoses available and transfusions in the outpatient clinic were similar to the results presented in the main manuscript (see supplemental material for detailed results).

DISCUSSION

The results of our analyses indicate that the time to the next transfusion decreases as the age of transfused platelet components increases. This decrease was found to be similar, ranging from 0.1 to 7.7 hours, for all buffy-coat-derived platelet components, irrespective of storage solution. Conversely, storage time was not associated with a reduced time to the next transfusion after transfusion of apheresis platelets. The total decrease in the time to next transfusion for buffy-coat derived platelets was a quarter of a day when comparing platelets stored for three days or less to those stored for six or seven days. This difference represents on average 0.25 transfusions per patient's admission.

Although this average of 0.25 less transfusions per admission may not seem to have clinical significance at the individual patient level, since 0.25 units of platelets are never transfused. This figure was estimated at the population level, meaning that some patients will receive one or more units less, while others may not benefit at all.

Table 4: Projected mean difference of total number of transfusions per admission

	Time to the next transfusion (in days)	One transfusion each (days in one admission)*	Difference (days in one admission)
Buffy coat-derived platelets in plasma			
1 to 3 days	3.494	3.18 days	reference
4 or 5 days	3.349	3.31 days	0.14 days
6 or 7 days	3.234	3.43 days	0.26 days
Buffy coat-derived platelets in plasma - hyperconcentrated			
1 to 3 days	3.466	3.20 days	reference
4 or 5 days	3.312	3.35 days	0.15 days
6 or 7 days	NA	NA	NA
Buffy coat-derived platelets in PAS-C			
1 to 3 days	3.100	3.58 days	reference
4 or 5 days	3.095	3.59 days	0.01 days
6 or 7 days	2.937	3.78 days	0.20 days
Buffy coat-derived platelets in PAS-B			
1 to 3 days	3.478	3.19 days	reference
4 or 5 days	3.156	3.52 days	0.33 days
6 or 7 days	NA	NA	NA
Apheresis platelets in plasma			
1 to 3 days	3.289	3.37 days	reference
4 or 5 days	3.093	3.59 days	0.21 days
6 or 7 days	3.214	3.45 days	0.08 days
Apheresis platelets in plasma - hyperconcentrated			
1 to 3 days	3.121	3.56 days	reference
4 or 5 days	3.120	3.56 days	0.00 days
6 or 7 days	NA	NA	NA

* $\left(\frac{\text{time to the next transfusions}}{\text{average length of admission (11.1 days)}}\right)$

NA: not available

Therefore, the positive clinical implications of the increased time between platelet transfusions observed for fresher platelet transfusions are the same as those for a decreased number of transfusions: less acute hemolytic reactions, febrile non-hemolytic reactions, risk of bacterial contamination, transfusion related acute lung injury (TRALI), allergic reactions, and alloimmunization.[26]

Conversely, transfusing only fresh or intermediate aged platelets (i.e. up to five days of storage) would severely affect the outdating and consequently increase the wastage. In the Netherlands it was shown that the outdating decreased from 20% to 10% when the maximum shelf-life of platelets in plasma was increased from five to seven days, corresponding to a preservation of 5,900 components yearly.[22,27]

It is important to realize that a policy of transfusing only fresh platelets to hematological patients would save 7% of these patients' platelet transfusions only when compared to transfusing only old platelets. However, the extended shelf-life of up to seven days does not make all platelets components old, but merely a fraction of them. In our study 27% of the transfused platelets were old (>5 days). Additionally, this gain only applies to hematological stable patients who account for 75% of the platelet transfusions.[17] Thus, the real gain would be a reduction of 1.4% of the total of platelet transfusions given (i.e. 7%×27%×75%) while an extra 10% of all platelet components would be wasted due to out-dating.[27] This results in an increased need for platelet components of about 8.6%.

Our results corroborate recent meta-analyses in which an overall difference in time to the next transfusion between old and new components of 0.25 days (i.e. six hours) for all components combined is reported.[3,4] In the present study the difference in time to the next transfusion between fresh and old platelets varies from 0.2 hours up to 6.2 hours depending on the component type. In the previous meta-analyses, there was no indication of substantial differences between studies investigating buffy coat-derived platelets and studies investigating apheresis platelets. However, the meta-analyses did not include sufficient studies to be able to stratify results per component type, as the present study did. In the current study no association between storage time and time to the next transfusion for apheresis platelets is observed. Besides reflecting a true difference between components this may also be the result of the specific indications for which apheresis platelets are prescribed in the Netherlands (i.e. HLA or HPA typed platelets, neonates, and adults in case of: ABO incompatibility, volume overload, or allergic reactions).[23]

Important strengths of our study are the size of the cohort and the use of a validated algorithm to select the patients of interest. By selecting the patients according to strictly defined transfusion patterns, we included patients whose time to the next transfusion depended on platelet counts. We thereby avoided selecting patients with pre-determined transfusion schedules and patients with insufficient response to platelet transfusions (refractory patients). Our algorithm had excellent performance (high specificity) for the overall population and also for each hospital studied. Patients selected by the algorithm with others than hematological diseases only received general diagnoses codes, like "care trajectory" or "inter-collegial consultation". These patients are potentially (and likely) hemato-oncological patients, who were transfused before a definitive diagnosis was made and recorded in the diagnosis system and consequently in our study database.

A potential limitation of this study is that we did not have information about the hour of the day at which donations and transfusions occurred.

Thus, estimation of the storage time and transfusion interval was only possible in whole days and therefore imprecise. On average, however, donations and transfusions occur mostly in the same time of the day. As a consequence the storage time and interval between transfusions tend to be, most of the time, not far from the presented results.

A seemingly limiting aspect of our study was the lack of diagnoses recorded in one of the databases. However, our sensitivity analyses of only patients with the diagnoses available showed results almost identical to those obtained from the full cohort. We are therefore confident that our algorithm selected the correct patient population allowing us to increase our sample size from 16,927 patients with diagnoses to 29,761 patients in the final database.In conclusion the present study showed that the transfusions interval decreases as the age of transfused platelet components increases, which seems similar for all buffy coat-derived platelet components and irrespective of storage solution. We also show that this decrease is unlikely to outweigh the benefit of reduced outdating and wastage, known to be associated with extended storage times. Furthermore, no decrease in transfusion interval was observed for apheresis platelets, which in the Netherlands are only prescribed for specific indications.

SUPPLEMENTAL MATERIAL

Available at: https://goo.gl/uDPNvD

- Predictive marginal per blood components and patients sex and age
- Examples of selection and period definitions
- DBC hematological codes and descriptions

Sensitivity analyses:

- Single storage age transfusion periods
- No outpatient clinic patients
- Age stratification
- Only patients with hematological diagnoses

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