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Effect of storage of platelet concentrates in PAS-B, PAS-C or plasma on transfusion reactions

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Abstract

BACKGROUND

Reports on the clinical consequences of longer storage time of platelet concentrates are contradictory. The objective of this study was to assess whether longer storage times are associated with a higher risk of transfusion reactions.

STUDY DESIGN AND METHODS

We gathered storage times of pooled platelet concentrates related to transfusion reactions reported to the national hemovigilance office from 2004 to 2015. These were combined with storage times of platelet concentrates in the reference population to compare incidences of transfusion-associated circulatory overload, transfusion-related acute lung injury, allergic, febrile non-hemolytic and "other" reactions between storage time categories.

RESULTS

A total of 567,053 platelet concentrates and 1,870 transfusion reactions were analyzed. Among PAS-B-platelet recipients, the **odds ratio** of a storage time of 4-5 compared to 1-3 days was 1.60 (95% confidence interval 1.17;2.18) for allergic, and 1.47 (1.09;1.98) for febrile reactions. For PAS-C-platelet recipients, the **odds ratio** for allergic reactions was 3.78 (1.31;10.9) for 4-5 days, and 4.57 (1.57;13.4) for 6-7 days old platelets when compared to 1-3 days old units. In all other studied reaction types no statistically significant association was observed in platelets in plasma, PAS-B and PAS-C.

CONCLUSIONS

In plasma-platelets storage time was not associated with a higher incidence of transfusion reactions. In PAS-platelets longer storage time was associated with higher transfusion reaction incidences, in particular for allergic reactions with both PAS-fluids and febrile reactions with PAS-B. This indicates that the effect of storage time is different for different reaction types and depends on the storage fluid.

Keywords: platelet transfusion, storage time, transfusion reaction, allergic reaction, FNHTR, TRALI, TACO

INTRODUCTION

Platelet transfusions are used to provide hemostatic capacity in patients with a decreased number or functionality of platelets.[1] However, platelet transfusions can cause adverse events as well, such as allergic, febrile non-hemolytic, transfusion-associated circulatory overload, transfusion-related acute lung injury and other reactions. All transfusion reactions cause some degree of inconvenience for patients and involve increased costs, and may result in (severe) morbidity, or even mortality.[2,3] Therefore, over the past decades extensive effort has been made to identify the factors contributing to the occurrence of transfusion reactions. Multiple factors, such as storage fluid, leukoreduction, collection method (apheresis or pooled buffy coats), and storage time have been studied for their roles in inducing transfusion reactions after platelet transfusions.[2,4,5] As a result of these earlier findings multiple improvements, such as leukoreduction, have been achieved in the production of platelet concentrates.[6,7] Nevertheless, platelet transfusions are still associated with relatively high incidences of transfusions reactions.

Storage time has been associated with the accumulation of biological response modifiers, such as inflammatory cytokines and chemokines.[8-11] Whether these changes also have clinical consequences is not clear yet, as published results are contradictory.[5,12] A recently published review paper concludes that the risk of transfusion reactions was similar in old, compared to fresh, leukoreduced units,[13] whereas a more recent study, not included in the review, showed that prolonged storage of platelets was associated with a higher frequency of inflammatory transfusion reactions, but not of allergic reactions.[12]

This controversy indicates that a better understanding of the influence of storage time on the development of transfusion reactions is warranted, and will create the opportunity to further improve transfusion safety.[2,14-17] Therefore, the objective of this study was to assess the association of storage time of leuko-reduced buffy-coat platelets stored in plasma, PAS B, or PAS C with the incidence of allergic reactions, febrile non-hemolytic reactions, transfusion-associated circulatory overload, transfusion-related acute lung injury and “other reactions”.

MATERIAL AND METHODS

Study design

This nationwide, case-referent study evaluated the impact of storage time of platelets on transfusion reaction rates in the period from 2004 to 2015.[18] Anonymized data, further described below, were obtained from the national hemovigilance organization 'Transfusion and Transplantation Reactions in Patients' (TRIP) and the national Sanquin database (ePrognosa, MAKsystems, Paris, France). The reference distribution of the storage time of all transfused platelet units was estimated using a database, as described earlier, containing data of more than 100,000 pooled platelet units transfused in the Netherlands.[19]

Platelet products and storage time

All platelet products, pre-storage leuko-reduced by filtration, were produced and stored by Sanquin Blood Bank (Amsterdam, the Netherlands). About 90% of platelet concentrates were prepared using five ABO identical and Rh-D compatible buffy coats from whole blood donations. These five buffy coats, each containing up to 30 mL of plasma, were re-suspended either in plasma of one of the five donors (plasma-platelets; January 1, 2006 until December 31, 2015) or in platelet additive solution (PAS-platelets). Two types of PAS were used during the studied period: PAS-B (also known as PAS-2 or T-Sol, Baxter (Nivelles, France), January 1, 2004 - November 30, 2012) and PAS-C (also known as PAS-III or Intersol, Fenwal, a Fresenius company (La Châtre, France) December 1, 2012 - December 31, 2015). The remaining 10% of platelet units were collected by apheresis. Apheresis and hyper-concentrated platelet units were excluded from this analysis, since these are transfused for specific indications, including previous transfusion reactions. The maximum storage time was 7 days for plasma- and PAS-C-platelets and 5 days for PAS-B-platelets. The total numbers of distributed units per type of platelet product over the studied periods in the Netherlands were obtained from the national Sanquin database (eProgresa). The storage time of the platelet units involved in reactions was calculated by subtracting the date of the blood donation, based on the eProgresa database, from the date of transfusion, based on the TRIP database. The storage times were classified in the three categories 1 to 3 days, 4 to 5 days and 6 to 7 days.

Hemovigilance system

All data on the transfusion reactions were obtained from TRIP. TRIP is the hemovigilance system in the Netherlands that has been operational since 2003.[20] Participation of a hospital is regarded as the professional standard both in the national transfusion guideline and by the Healthcare Inspectorate.[21] 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 90% each year from 2004.[20] We evaluated transfusion reactions, reported between January 1, 2004, and December 31, 2015 for which the storage time of the platelet units could be determined. The definitions of reportable reaction types have previously been published.[20] These are mostly similar to the international definitions developed by the International Hemovigilance Network in collaboration with the International Society for Blood Transfusion.[22] In these definitions, febrile non-hemolytic transfusion reactions (FNHTRs) and mild FNHTRs are recorded 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. Mild FNHTRs were excluded from our analyses, because not all hospitals report mild FNHTRs to TRIP. The reaction type “allergic reaction” included both anaphylactic reactions and other allergic reactions. (Suspected) bacterial and viral transfusion transmitted infections were excluded as these have been reported elsewhere.[19] 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. Furthermore, only reactions with imputability “certain”, “probable” or “possible” were included in our analyses. If multiple units of platelets were associated with a reaction, the reaction was included only if the units were in the same storage time category.

Statistical analyses

The association of storage time with transfusion reaction incidences was assessed separately for each of the three platelet storage media (PAS-B, PAS-C and plasma), because the maximal storage period and thereby the distribution of the storage times differs. Moreover, differences are observed between the storage media regarding the associated transfusion reaction incidences. Most importantly, there might also be effect modification by the storage medium. The effect of storage time on transfusion reaction incidences was evaluated using logistic regression derived odds ratios with 95% confidence intervals (CIs). Hospital could be a confounder in our analyses, because hospital is correlated both with the storage time distribution and with the reported transfusion reaction rate. The

distribution of storage time of transfused blood products might differ between hospitals because of differences in location, scale, patient population and policy. The rate of reported transfusion reactions of hospitals may be influenced by transfusion policy and practice, patient population, hospital reporting instructions as well as culture. To correct for confounding by hospital, weighting was performed based on the hospital's reporting tendency. As all Dutch hospitals use the same type of red blood cell units, the incidence of reported transfusion reactions following RBC transfusions was used as a measure for reporting tendency of the hospital. For university hospitals the incidences were calculated separately for every hospital. As in several non-university hospitals the incidence of RBC transfusion reactions is very low and often close to zero, which would give unstable and unrealistic weights, the weight for the non-university hospitals was calculated for the whole group of non-university hospitals. All incidences of the hospital (group) were divided by the national incidence, and then the inverse of this ratio was used as a weight. The transfusion reactions were weighted by these calculated inverses in our analyses. This can be summarized in the following equation:

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

RESULTS

Population

A total of 567,053 pooled platelet units and 1,870 transfusion reactions were analyzed in our study (shown in table 1). The majority of the 1,870 transfusion reactions, 1081 (57.8%), were allergic reactions, 547 (29.3%) were febrile reactions, 39 (2.1%) were cases of transfusion-associated circulatory overload, 24 (1.3%) were cases of transfusion-related acute lung injury, and 179 (9.6%) were classified as “other reaction”. From 2006 to 2015 a total of 425,127 plasma-platelet units were distributed and during this period 1,472 transfusion reactions were reported to TRIP that followed transfusion of plasma-platelets. In the period from 2004 to 2012 a total of 96,669 PAS-B-platelet units were distributed, and 297 reactions were reported that were associated with PAS-B-platelet transfusions. From 2012 to 2015, 45,227 units of PAS-C-platelets were distributed, and 101 reactions associated with PAS-C-platelet transfusions were reported. The crude, unweighted incidences per storage fluid per storage time category and overall incidences are reported in the supporting information.

Storage time and transfusion reactions

For plasma-platelets the **odds ratios** per reaction type per storage time category compared to the reference category are shown in table 2. In patients receiving plasma-platelets no differences were observed between older and fresher units for any of the specified reactions. In PAS-B platelets, shown in table 3, the transfusions with older (4 to 5 day old) units were associated with more allergic reactions compared to the fresher (1 to 3 day old) units, **odds ratio** 1.60 (1.17;2.18). Also, the older PAS-B-platelets were associated with more FNHTRs than the fresher units, **odds ratio** 1.47 (1.09;1.98). No statistically significant differences were observed between older and fresher units in PAS-B for the other reaction types. In PAS-C-platelets transfusions with older units were also associated with more allergic reactions (table 4). Units with a storage time of 4 to 5 days (**odds ratio** 3.78, 1.31;10.9), as well as units of 6 to 7 days, **odds ratio** (4.57, 1.57;13.3), were both associated with more allergic reactions compared to the reference group. No statistically significant differences were observed between older and fresher PAS-C units for the other reaction types. The **odds ratios** found in the crude unweighted analysis were comparable to the results of the weighted analysis (supporting information).

DISCUSSION

In this nationwide study, older PAS-B-platelets were associated with a higher incidence of allergic and febrile reactions. Among PAS-C-platelets, the older units were associated with a higher allergic reaction incidence compared to fresh units. In plasma-platelets, no statistically significant differences were observed between fresher and older units with regard to any of the transfusion reactions.

Strengths and limitations

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 leuko-reduced platelets. Moreover, our analysis included over half a million platelet transfusions, which made it possible to analyze the different platelet products and reaction types separately. Furthermore, in our study it was possible to estimate the effect of storage time on transfusion reactions with great precision. A limitation of our study was that the distribution of the storage time of all transfused platelet units was estimated based on a subset of the Dutch hospitals. It is possible that this dataset is not completely representative for the source population. However, data of more than 100,000 transfusions are included of both university and large general hospitals located in different regions of the Netherlands. So, large, systematic deviations from the source population are unlikely. Also, not all transfusion reactions could be included in the analysis as not all storage times could be determined. However, we do not believe that this poses a considerable problem as we do not expect an association between the storage time of a product and the chance that the storage could be determined. **In our database no patient identifier was available, so it was impossible to correct for the potential influence of patient level dependency. However, it is unlikely that this had significant influence on the studied association as there is no reason to assume that both storage time and transfusion reactions cluster at patient level.** 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 are probably the most relevant reactions.

Plasma-platelets

It has been demonstrated that older platelets show *in vitro* deterioration and in transfused patients result in inferior laboratory measurements (like corrected count increments) compared to fresher

platelets.[23,24] However, the clinical impact on patient outcomes, like transfusion reactions, is not clear yet. A recent meta-analysis summarizing the effect of storage time on clinical outcomes concluded that older platelet products were associated with more transfusion reactions.[5] However, the increased risk of reactions was not observed when leuko-reduced products were analyzed separately, which is in agreement with our findings in plasma-platelets. As our study contains a considerably larger sample size, our findings strengthen the plausibility of the earlier findings for plasma-platelets.[25,26] Another recent study showed that prolonged storage of plasma-platelets was associated with more inflammatory transfusion reactions (including FNHTRs, TRALI, transfusion associated dyspnea and atypical reactions), but not with allergic reactions.[12] Regarding allergic reactions this other study is in agreement with our study. However, the association in this study between storage time and inflammatory reactions was not confirmed in our study. In the other study not only storage time, but also irradiation and the collection method apheresis were strongly associated with inflammatory reactions. The finding that apheresis as collection method is associated with more transfusion reactions than pooled leuko-reduced platelets is affirmed by others.[2] The fact that apheresis seems to increase the incidence of transfusion reactions, may explain that this other study found an association between storage time and inflammatory reactions in apheresis plasma-platelets while in our study we found no association in pooled plasma-platelets.

PAS-platelets

The findings of the earlier mentioned meta-analysis are not in agreement with our findings in PAS-platelets. However, the meta-analysis pooled all results irrespective of reaction type; storage fluid; collection method; which storage days were compared and the patient population.

In PAS-B-platelets we found that a longer storage time was associated with a higher incidence of both allergic and febrile reactions. To the best of our knowledge our study is the first clinical study regarding the effect of storage time on allergic and febrile reactions in leuko-reduced PAS-B-platelets.

For PAS-C-platelets we found that storage for 6 to 7 days was associated with a higher overall incidence of transfusion reactions. In the SPRINT trial, both pathogen-reduced and conventional apheresis platelet concentrates were analysed. Based on these data, a **odds ratio** of 2.36 (1.33;4.19) was calculated in the previously described meta-analysis for 4 - 5 days old conventional platelets compared to 1 - 2 days old conventional platelets in PAS-C.[5,27] Although this study reported on

apheresis platelets and our study on pooled buffy-coat platelets, these findings are in agreement with each other. Another recent study regarding platelets in PAS-E (SSP+) is less comparable, because only absolute numbers were reported, and because different storage time categories were compared.[28] In a study of platelets in PAS-F (Plasmalyte), a clear association between storage time and transfusion reactions was demonstrated.[29] Not all these platelets were pre-storage leuko-reduced, but the leukoreduction status was one of the factors that was considered in their statistical model so the reported association between storage time and transfusion reactions was calculated independently of the leukoreduction status. Although Plasmalyte is not the same storage fluid as PAS-B and PAS-C, the findings about the effect of storage time on transfusions reactions are in line with our results.

For PAS-B-platelets, storage time was statistically significantly associated with febrile reactions, but for PAS-C-platelets the association was not observed. Only the **odds ratio** of the oldest category pointed in the same direction, which may be due to a lack of statistical power in the analyses on PAS-C-platelets, but it is also possible that this indicates that platelets in PAS-C are actually more stable during storage.

Clinical implications

In conclusion, in plasma-platelets, storage time is not associated with a higher incidence of transfusion reactions. In PAS-platelets, storage time is associated with higher transfusion reaction incidences, in particular with allergic reactions in both PAS-fluids, and with febrile reactions in PAS-B. Although in plasma-platelets no association was observed between longer storage time and more transfusion reactions, the overall incidence of transfusion reactions following plasma-platelets is still comparable to that of PAS-B-platelets and higher than that of PAS-C-platelets as we showed earlier.[4] So regarding transfusion reactions it seems that platelets stored in PAS-C are the best option. However, the fact that the incidence of transfusion reactions increases over storage time may mean that also for PAS-C there is room for improvement.

For clinical practice not only the risk of adverse events like transfusion reactions, but also the haemostatic efficacy of platelet concentrates should be taken into account. Earlier we showed *in vitro*, in reconstituted whole blood, that the function of PAS-C-platelets seems inferior to the function of plasma-platelets.[30] However, it is not clear whether this affects patient outcomes in clinical practice.

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Author contributions

F.M.A. van Hout designed the study, analyzed an interpreted the data and wrote the manuscript; R.A. Middelburg, P.F. van der Meer, J.G. van der Bom and J.L. Kerkhoffs contributed to the study design, and critically reviewed the manuscript; J.C. Wiersum-Osselton contributed to the acquisition of the data, to the study design, and critically reviewed the manuscript, A. Pors contributed to data management and study design, and critically reviewed the manuscript, and M.R. Schipperus contributed to the acquisition of the data and critically reviewed the manuscript.

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Tables

Table 1 Crude number of distributed platelet concentrates and reported transfusion reactions per storage fluid

	Storage fluid		
	plasma	**PAS-B**	**PAS-C**
Transfusions			
Total number of transfusions	425,127	96,699	45,227
Mean storage time (days)	4.74	3.45	4.50
Median (IQR) storage time (days)	5 (3 - 6)	3 (2 - 4)	4 (3 - 6)
Reactions			
Total number	1,472	297	101
Per storage time category			
- **1 - 3 days**	**387**	**120**	**21**
- **4 - 5 days**	**512**	**177**	**37**
- **6 - 7 days**	**573**		**43**
Mean storage time (days)	4.78	3.69	5.04
Median (IQR*) storage time (days)	5 (3 - 6)	4 (3 - 5)	5 (4 - 6)
Years included	2006 - 2015	2004 - 2012	2012 - 2015

* IQR interquartile range

Table 2 Odds ratios (with 95% CI) for transfusion reactions after platelet concentrate transfusion: old versus fresh units

Plasma-platelets	**Storage time**		
Reaction type	**1 - 3 days**	**4 - 5 days**	**6 - 7 days**
Allergic reaction	reference	0.95 (0.81;1.13)	1.02 (0.87;1.21)
FNHTR	reference	1.07 (0.82;1.39)	1.15 (0.89;1.49)
TRALI	reference	1.56 (0.50;4.80)	1.44 (0.46;4.52)
TACO	reference	0.45 (0.18;1.15)	0.78 (0.35;1.75)
Other reaction	reference	0.82 (0.53;1.28)	1.13 (0.75;1.71)
Overall	reference	0.96 (0.84;1.10)	1.06 (0.93;1.21)
PAS-B-platelets	**Storage time**		
Reaction type	**1 - 3 days**	**4 - 5 days**	
Allergic reaction	reference	1.60 (1.17;2.18)	
FNHTR	reference	1.47 (1.09;1.98)	
TRALI	reference	NA	
TACO	reference	1.56 (0.43;5.67)	
Other reaction	reference	1.44 (0.69;3.02)	
Overall	reference	1.54 (1.26;1.89)	
PAS-C-platelets	**Storage time**		
Reaction type	**1 - 3 days**	**4 - 5 days**	**6 - 7 days**
Allergic reaction	reference	3.78 (1.31;10.9)	4.57 (1.57;13.3)
FNHTR	reference	0.90 (0.37;2.19)	1.93 (0.86;4.31)
TRALI	reference	NA	NA
TACO	reference	0.56 (0.04;7.31)	NA
Other reaction	reference	0.60 (0.16;2.24)	0.73 (0.19;2.77)
Overall	reference	1.41 (0.81;2.44)	2.03 (1.18;3.49)

Odds ratios with 95% confidence interval, weighted for reporting rate, with storage time of 1 to 3 days as the reference category.

FNHTR non-hemolytic transfusion reaction; NA not applicable; TACO transfusion-associated circulatory overload; TRALI transfusion-related acute lung injury

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Supporting information

Table S1 Crude, unweighted incidences of transfusion reactions per storage fluid per storage time category

	Storage time			
Storage fluid	**1 - 3 days**	**4 - 5 days**	**6 - 7 days**	**overall**
plasma	0.346	0.327	0.366	0.346
PAS-B	0.241	0.377	not applicable	0.307
PAS-C	0.154	0.208	0.312	0.223

Absolute, unweighted incidences per 100

Table S2 Crude (unweighted) odds ratios (with 95% CI) for transfusion reactions after platelet concentrate transfusion: old versus fresh units

Plasma-platelets	**Storage time**		
Reaction type	**1 - 3 days**	**4 - 5 days**	**6 - 7 days**
Allergic reaction	reference	0.93 (0.79;1.10)	1.01 (0.85;1.19)
FNHTR	reference	1.05 (0.80;1.36)	1.15 (0.88;1.49)
TRALI	reference	1.14 (0.37;3.48)	1.28 (0.43;3.83)
TACO	reference	0.50 (0.19;1.31)	0.86 (0.37;1.98)
Other reaction	reference	0.85 (0.55;1.31)	1.18 (0.78;1.77)
Overall	reference	0.94 (0.83;1.08)	1.06 (0.93;1.20)
PAS-B-platelets	**Storage time**		
Reaction type	**1 - 3 days**	**4 - 5 days**	
Allergic reaction	reference	1.66 (1.17;2.36)	
FNHTR	reference	1.46 (1.03;2.05)	
TRALI	reference	NA	
TACO	reference	1.41 (0.32;6.30)	
Other reaction	reference	1.48 (0.66;3.33)	
Overall	reference	1.56 (1.24;1.97)	
PAS-C-platelets	**Storage time**		
Reaction type	**1 - 3 days**	**4 - 5 days**	**6 - 7 days**
Allergic reaction	reference	3.21 (1.21;8.52)	3.95 (1.48;10.5)
FNHTR	reference	0.93 (0.39;2.26)	2.09 (0.94;4.61)
TRALI	reference	NA	NA
TACO	reference	0.38 (0.04;4.21)	NA
Other reaction	reference	0.61 (0.16;2.28)	0.79 (0.21;2.94)
Overall	reference	1.35 (0.79;2.30)	2.02 (1.20;3.41)

Crude **odds ratios** with 95% confidence interval, not weighted for reporting rate, with storage time of 1 to 3 days as the reference category.

FNHTR non-hemolytic transfusion reaction; NA not applicable; TACO transfusion-associated circulatory overload; TRALI transfusion-related acute lung injury