Chapter 6

Effect of storage time of platelet products on clinical outcomes after transfusion: a systematic review and meta-analyses

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Abstract

Background

Prolonged storage improves the availability of platelet products, but could also influence safety and efficacy. This systematic review and meta-analyses summarizes and quantifies the evidence of the effect of storage time of transfused platelets on clinical outcomes.

Methods

A systematic search in seven databases was performed up to February 2016. All studies reporting storage time of platelet products and clinical outcomes were included. To quantify heterogeneity, I^2 was calculated, and to assess publication bias, funnel plots were constructed.

Results

Twenty-three studies reported safety outcomes and fifteen efficacy outcomes. The relative risk of a transfusion reaction after old platelets compared to fresh platelets was 1.53 (95% confidence interval (CI): 1.04 to 2.25) (12 studies). This was 2.05 (CI 1.47 to 2.85) before and 1.05 (CI 0.60 to 1.84) after implementation of universal leukoreduction. The relative risk of bleeding was 1.13 (CI 0.97 to 1.32) for old platelets compared to fresh (5 studies). The transfusion interval was 0.25 days (CI: 0.13; 0.38) shorter after transfusion of old platelets (4 studies). Three studies reported use of platelet products, two for hematological patients, one for trauma patients. Selecting only studies in hematological patients, the difference was 4.51 units (CI1.92; 7.11).

Conclusion

Old platelets increase the risk of transfusion reactions in the setting of non-leukoreduction, shorten platelet transfusion intervals, thereby increasing the numbers of platelet transfusions in hematological patients, and may increase the risk of bleeding.

Introduction

Platelets are transfused to prevent or treat bleeding complications in patients with thrombocytopenia or platelet dysfunction.[1] Platelet products can be stored for a maximum of 4-7 days, depending on national guidelines and type of product.[2-5] During the period 2000-2002, a survey found the mean annual discard rate for 17 blood banks in 10 countries to be 13% (range 6.7-25%). As outdating was the main reason for discarding platelet products, prolonging storage is likely to reduce the number of discarded units.[6] However, *in vitro* studies demonstrated a gradual loss of platelet function during storage at room temperature, which is known as the 'storage lesion'.[7]

We previously performed a systematic review and meta-analyses on the effect of storage time at room temperature on clinical measurements. In these meta-analyses, older platelets had inferior results on all endpoints as compared to fresher products.[8] However, the clinical implications of these effects are not clear.[9,10] Therefore, the aim of the current systematic review and meta-analyses is to quantify the effect of storage time of platelet products on clinical outcomes after transfusion.

Methods

The search strategy, study selection, methods for assessing the risk of bias, and the data extraction were described previously and are in accordance with a pre-specified study protocol.[8]

Search strategy

In brief, a systematic search was applied to seven databases: MEDLINE (Pubmed), EMBASE, Cochrane, CINAHL, Academic Search Premier, ScienceDirect and Web of Science. Results were checked for missing relevant papers by experts in the field and the search strategy was adapted as needed. The search was last updated and performed in February 2016. The search strategy contained synonyms for platelets, fresh, old, and storage time. No limitations were placed on study design, language or year of publication (supplemental material).

Study selection

As specified in the study protocol, two reviewers independently screened titles and abstracts for relevance. Inclusion criteria were: performed in humans, concerning platelet transfusion, reporting clinical outcomes, reporting different storage times, and reporting original data. Disagreements were discussed with a third reviewer. The risk of bias was scored according to the 'Cochrane Collaboration's tool for assessing risk of bias' for randomized controlled trials[11] and 'Fowkes & Fulton tool' for randomized controlled trials and observational studies.[12] The items in the Fowkes & Fulton tool are appropriate study design, representative study sample, acceptable control group, quality of measurements and outcome, completeness, and confounding, which is similar as in the ACROBAT NRSI Cochrane tool for assessing non-randomized studies.[13] Papers scoring insufficient on one of these items were excluded.

Studies could only be included in the meta-analyses if they reported both a point estimate and a measure of precision. Further, studies needed to report an effect measure which could be recalculated to allow pooling with data from other studies (e.g. some studies reported only mean storage time in cases and controls, whereas risk ratios were reported in other studies). Papers written in other languages than English were translated and data extraction was verified by native speakers.

Data extraction

Storage time, type of outcome, product type, point estimate, and measure of precision were recorded. Authors of included studies were contacted when additional information was needed. If necessary, original results were recalculated in order to enable pooling of the results. In all cases where the underlying distribution could be assumed to be normal, mean and standard deviation were calculated from median, range and quartiles.[14] Results expressed in hours were recalculated to days.

Categorization

Storage time was dichotomized into fresh and old. Where storage time was already dichotomized, the reported dichotomization was maintained. Most papers defined fresh as ≤3 days and old as ≥4 days. Therefore these definitions were used to summarize results if papers reported multiple storage time categories, using standard formulas for combining samples sizes (Σn_i), means ($\sum \bar{x}_i * n_i / (\sum n_i)$) and standard deviations ($SD = (\Sigma(n_i - 1)s_i^2 / sqrt[\Sigma(n_i - 1)]$) from multiple groups. Results were grouped by product: apheresis, pathogen-reduced apheresis (PR_aph), buffy coat in plasma (BC_plasma), buffy coat in platelet additive solution (BC_PAS),

pathogen reduced buffy coat in platelet additive solution (PR_BC PAS), and platelet rich plasma (PRP). If papers reported results concerning different products, these were handled as separate results.

Outcomes

Papers reporting laboratory measurements (i.e. corrected count increments, count increment, platelet recovery, survival, half-life) were reported elsewhere.[8]

Outcomes related to safety aspects were categorized into transfusion reactions, as defined by Delaney et al.;[15] complications, including other adverse events; mortality; and length of hospital stay. In-hospital mortality for trauma patients was assumed to be equivalent to 60 day mortality, if no additional data were available. In other words, we assumed that it was very unlikely that trauma patients who were discharged alive subsequently died within 60 days. The cut-off point of 60 days was chosen, as these data were available in other papers reporting mortality.

Outcomes related to efficacy aspects were categorized into bleeding; transfusion interval; transfusion need (i.e. number of platelet, red blood cell, and plasma transfusions, or amount of cryoprecipitate during hospital stay or period of five days, as reported); repeated transfusion within 24 hours; and hemostatic potential as measured by thromboelastography.

Statistical analyses

For studies reporting only incidences of transfusion reactions, complications, mortality, and bleeding, the relative risk was calculated using standard formulas.[16] The corresponding 95% confidence intervals were calculated using Fisher's exact test. Standard errors were determined from the confidence intervals. For case control studies, odds ratios were calculated with standard errors according to the formula of Woolf.[17] The included case control studies selected controls in a way which allowed the reported odds ratios to be interpreted as relative risks.[18] These odds ratios were therefore treated as relative risks in all analyses. Relative risks reflecting the risk of stoppage of bleeding, or improvement in bleeding rate were recalculated to reflect the risk of no stopping of bleeding or no improvement of bleeding rate.

For continuous outcomes, weighted mean differences (WMD) were calculated. If more than ten studies were included, a pre-specified subgroup analysis was performed, based on product type (i.e. before or after implementation of universal leukoreduction). Metaregression was performed to examine the impact of product type on the pooled estimate. The adjusted R-squared ($R^2_{adj} = (\hat{\tau}_0^2 - \hat{\tau}^2)/\hat{\tau}_0^2$) was calculated to examine the proportion of heterogeneity explained by product type. A

sensitivity analysis was performed, excluding the studies with the largest standard errors and meeting abstracts.

To assess the risk of publication bias, funnel plots were generated and Egger's bias coefficient was calculated.[19] A single funnel plot was made for all continuous endpoints combined. To standardize all outcomes to the same scale, the standardized mean difference (SMD) was calculated for each comparison. The standardized mean difference expresses the size of the intervention effect in each comparison relative to the standard deviation estimated in that comparison.[20] All studies were centered around the point of no effect by subtracting the pooled standardized mean difference for each outcome from the standardized mean difference for that outcome of each comparison.

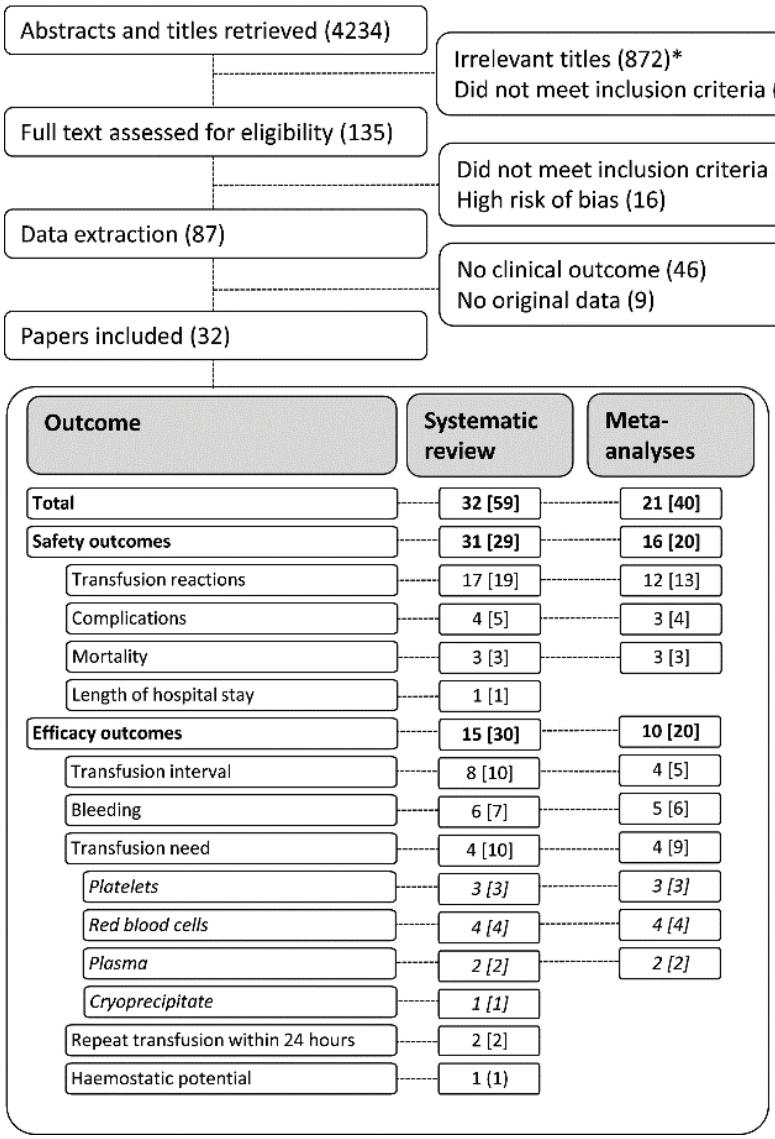
Heterogeneity was quantified by the I^2 statistic.[21] To account for substantial heterogeneity a random effects model was used for all meta-analyses. As a sensitivity analysis, we performed a meta-analysis including only the observational studies. All statistical analyses were performed using Stata version 14, packages metan and metareg.

Results

Selection

The literature search yielded 4,234 papers, of which title and abstract were screened for the predefined inclusion criteria, as described previously.[8] Following selection on inclusion criteria and the risk of bias, 32 studies, reporting 59 unique comparisons, were included in this systematic review (figure 1). This included five meeting abstracts and 27 original papers. Four papers reported on trials in which storage time was randomized. Twenty-three studies reported on observational cohort studies, of which five were secondary analyses on data of randomized trials. Five papers reported on case control studies. Thirty-one papers were written in English and one in Chinese. Included studies are described in more detail in the supplemental material, table S1.

Figure 1. Flow chart of study selection



Numbers represent numbers of papers. Some papers reported comparisons for more than one outcome or multiple comparisons for a single outcome. Numbers in square brackets represent the number of unique comparisons.

Table 1. Description of studies retrieved by the literature search, but not reporting data necessary for pooling in the meta-analyses.

Author and year	Product[a]	Definition fresh	Favours old	No difference	Favours fresh	Definition old	Group size fresh vs. old [*N* transfusions][b]	Outcome (fresh vs. old or controls vs. cases)
Transfusion reactions								
Heddle 1993	PRP or Aph	1–3				4–5	Total 65 transfusions	Slope logistic regression $P = 0{,}004$[c]
Lane 1997	Aph	3·1				3·8	36 controls vs. 9 cases	3·1 ± 1·1 vs. 3·8 ± 0·7 days[d]
Patterson 2000	PRP_nonL	≤3				>3	338 vs. 789 transfusions	Slope linear regression 0·0305; $P < 0{\cdot}001$[c]
Silliman 2003	PRP or Aph	4·2				4·5	225 controls vs. 46 cases	4·2 ± 0·1 vs. 4·5 ± 0·2 days, $P = 0{\cdot}014$[d]
Patterson 2000	PRP	≤3				>3	306 vs. 1023 transfusions	Slope linear regression 0·009; $P = 0{\cdot}5$[c]
Liu 2013	Aph	2·87				2·92	13 controls vs. 16 cases	2·87 ± 0·82 days vs. 2·92 ± 1·03[d]
Complications								
Vande Vusse 2014	PRP or Aph						906 patients, 75 cases	HR: 0·84 (CI: 0·51–1·37)[c]
Length of ICU stay								
Inaba 2011	Aph	≤3				4–5	128 [205] vs. 253 [380] patients	Median 6 (range 1–181) vs. 6 (1–181) days
Shorter interval between transfusions								
Norol 1994	Aph	≤8 h				≤2	141 [141] vs. 141 [141] patients	3·1 vs. 2·3 days
Benjamin 2003	Aph	1–2				4–5	697 vs. 1247 transfusions	2·0 vs. 2·0 days; $P = 0{\cdot}97$
Benjamin 2003	PR_aph	1–2				4–5	383 vs. 1176 transfusions	1·4 vs. 1·6 days; $P = 0{\cdot}18$
Heuft 2013	Aph	1–4				1–5	36 [191] vs. 41 [250] patients	2·0 vs. 1·1 days; $P < 0{,}001$
Slichter 2005	PRP or Aph	<2				3–5	Total 5423 transfusions in 525 patients	Difference 0·19 days (CI: 0·12–0·26)
Time to first who ≥2 bleeding								
Triulzi 2012	BC or Aph	3				5	156 vs. 217 patients	HR: 1·02 (CI: 0·62–1·70)
Transfusion need: cryoprecipitate								
Inaba 2011	Aph	≤3				4–5	128 vs. 253 patients	Median 0 (range 0–33) vs. 0 (0–22) units
Repeated transfusion ≤24 h								
Norol 1994	Aph	≤8 h				≤2	88 vs. 88 transfusions	RR: 6·2 (CI: 2·5–15·4)
Duguid 1991	BC_plasma	1–2				3–5	77 vs. 40 transfusions	RR: 2·3 (CI: 1·1–4·8)
Haemostatic potential (TEG)[e]								
Roeloffzen 2010	BC_plasma	1–3				4–5	35 vs. 35 patients	*K*-time: 27 ± 16 vs. 37 ± 22 min $P = 0{\cdot}03$[e] Alpha angle: 13° ±10° vs. 8°±8° $P = 0{\cdot}02$

Studies can appear more than once if multiple products or multiple end-points were reported.

Studies were excluded from the meta-analyses if no measure of precision was reported or if effect measure could not be recalculated in order to allow pooling of results.

■ Conclusion of the paper. 'No difference' means paper found no relevant differences between the groups.

[a]Product codes: aph, apheresis; BC_plasma, buffy coat stored in plasma; PRP, platelet-rich plasma, nonL, non-leucoreduced; PR, pathogen reduced.

[b]Group size is expressed as number of patients [number transfusions], unless otherwise specified.

[c]Storage time analysed as categorical variable, per day.

[d]Storage time in controls vs. storage time in cases.

[e]Thromboelastography measurements: *K*-time: time until a fixed level of clot firmness is reached in minutes, Alpha angle: rate of clot growth in degrees.

Safety outcomes

Transfusion reactions

One randomized trial, two secondary analyses of randomized trials, nine cohort studies and five case control studies reported transfusion reactions (figure 1). In ten papers different kind of transfusion reactions were reported as one combined endpoint. In three papers transfusion reactions were specified as febrile non-hemolytic transfusion reactions, in two papers as transfusion related acute lung injury (TRALI), in one paper as allergic transfusion reactions, and in one paper as septic transfusion reactions.

Twelve studies (thirteen comparisons) were included in the meta-analysis. The pooled risk ratio of old versus fresh platelets was 1.53 (95% confidence interval (CI): 1.04 to 2.25, I^2 83.1%) (figure 2). Before universal leukoreduction was introduced this risk ratio was 2.05 (CI: 1.47 to 2.85, I2 55.6%) and after introduction it was 1.05 (CI 0.60 to 1.84, I2 80.8%). The relative risk ratio of leukoreduced products compared to non-leukoreduced products was 0.51 (CI: 0.31 to 0.86, I2 68.1%). Adjustment for leukoreduction explained 42.36% of heterogeneity. Eggers bias coefficient was 1.62 (p=0.26) (supplemental material). Selection of the observational studies yielded a relative risk of 1.05 (CI 0.57 to 1.92) (supplemental material). This was similar to the risk ratio in the randomized trial (RR 1.10, CI 0.22 to 5.40). An additional analysis excluding the meeting abstracts and smaller studies, gave similar results (supplemental material). Five studies (six comparisons) were excluded from the meta-analysis. Three were case control studies comparing mean storage time in both groups, one study did not report the group sizes, and one (two comparisons) only reported a regression coefficient. Of these six comparisons, two reported no difference in incidence of transfusion reactions between both storage time categories in leukoreduced products, three reported an increased incidence after exposure to older non-leukoreduced platelets, and one reported no difference of mean storage time in cases and controls who received leukoreduced as well as non-leukoreduced products (table 1).

Other safety outcomes

Four cohort studies reported complications. Reported complications were: major infections, defined as pneumonia, positive blood culture, leg wound infection, sternal wound infection, or mediastinitis; positive blood culture; idiopathic pneumonia syndrome; and a composite endpoint of sepsis, ARDS, renal failure, or liver failure. Three studies, four comparisons, were included in the meta-analysis. The pooled risk ratio for these complications of old versus fresh platelets was 1.07 (CI: 0.83; 1.38, I^2 66.6%) (figure 2). One paper could not be included in the meta-

analysis, as it reported a hazard ratio of risk of idiopathic pneumonia syndrome, which was 0.84 (CI 0.51 to 1.37).

One randomized trial and two cohort studies reported mortality.[22-24] All were included in the meta-analysis. The pooled risk ratio for mortality was 1.03, (CI: 0.86 to 1.24, I^2 0.0%) (figure 2). The pooled risk ratio in observational studies was 1.03 (CI 0.86 to 1.25) compared to 0.93 (CI 0.29 to 2.96) in the randomized trial was (supplemental material).

Length of ICU stay was reported by one study, which found no difference for trauma patients receiving fresh or old platelets.

Figure 2. Forest plot safety outcomes and platelet storage time

Panel A. Meta-analyses of transfusion reactions and platelet storage time, stratified by implementation of universal leukoreduction.

Panel B. Meta-analyses of complications and mortality and platelet storage time.

The numbers represent the relative risk of old platelets compared to fresh platelets with corresponding 95% confidence interval for each study.

** Product codes: Aph = apheresis, , PRP = platelet rich plasma, BC-PAS = buffy coat stored in PAS, BC-plasma = buffy coat stored in plasma PR = pathogen-reduced.*

† FNHTR = Febrile non haemolytic transfusion reaction.

‡ TRALI = Transfusion related acute lung injur

Efficacy outcomes

Transfusion interval

Three randomized trials, two secondary analyses of randomized trials and three cohort studies reported a transfusion interval. Four studies (five comparisons) were included in the meta-analysis. The interval between transfusions was 0.25 days (CI: 0.13 to 0.38, I^2 19.5%) longer after transfusion of fresh platelets (figure 3). The weighted mean difference in the observational studies was 0.19 days (CI 0.14 to 0.25) and in the two randomized trials it was 0.42 days (CI 0.10 to 0.75) (supplemental material). Four papers (five comparisons) were excluded from the pooled analysis, as these did not provide the necessary measure of precision. Three reported a longer interval following transfusion of fresh platelets. One paper reported no difference in interval following transfusion of apheresis platelet products and a shortened interval after transfusion of fresh pathogen reduced products (table 1). Using the number of transfusions per study as weighing factor, the mean interval reported by the papers excluded from the meta-analysis was 0.14 days.

Bleeding

Two randomized trials, two secondary analyses of randomized trials and two cohort studies reported data about bleeding. Reported bleeding endpoints were: incidence of any bleeding symptoms; incidence of bleeding in the central nervous system; percentage of transfusions resulting in lower WHO grade of bleeding; incidence of stopping of gastrointestinal bleeding, hemorrhagic cystitis or epistaxis; proportion of days with bleeding as measured by daily monitoring; and time from transfusion to first WHO grade 2 bleeding. In four studies patients were assessed for bleeding symptoms daily. In two studies medical records were reviewed for bleeding symptoms. Five studies (six comparisons) were included in the meta-analysis. The pooled risk ratio of old platelets versus fresh platelets for any bleeding symptom was 1.13 (CI: 0.97 to 1.32, I^2 38.4%). The pooled risk ratio in observational studies was 1.18 (CI 0.99 to 1.41) and in the two randomized trials the pooled risk ratio was 0.86 (CI 0.58 to 1.27) (supplemental material). Exclusion of the meeting abstracts gave similar results (supplemental material). One paper could not be included in the pooled analysis, as it reported the time to first ≥WHO grade 2 bleeding (hazard ratio old versus fresh: 1.02 CI: 0.62 to 1.70).

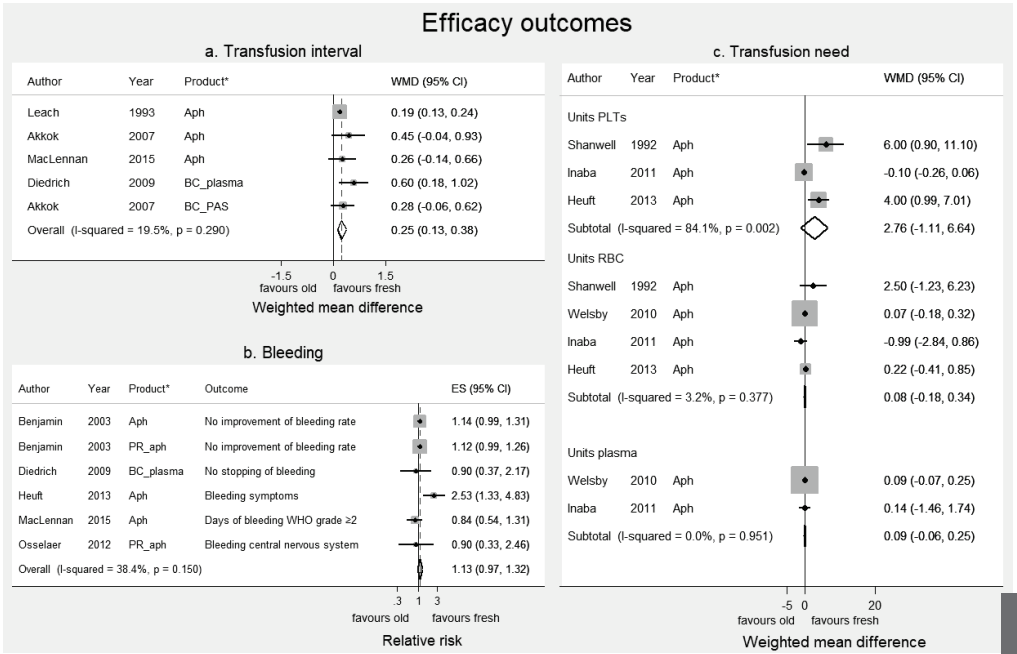
Transfusion need

One randomized trial and three cohort studies reported the need of transfusions. This was reported during hospital stay or during a period of five days. Three papers

(three comparisons) were included in the meta-analysis on need of platelet transfusion. The weighted mean difference was 2.76 fewer products (95% CI: -1.11 to 6.64, I^2 84.1%) with fresh platelets compared to old platelets (figure 3). Two studies were performed among hematological patients and one among trauma patients. Selecting only studies in hematological patients yields a weighted mean difference of 4.51 units (CI 1.92; 7.11). The weighted mean difference in the two observational studies was 1.66 units (CI -2.32 to 5.64), and in the randomized trial it was 6.00 units (CI 0.90 to 11.10) (supplemental material).
Four papers (four comparisons) were included in the meta-analysis on need of red blood cell transfusions. The weighted mean difference was 0.08 products fewer (95% CI: -0.18 to 0.34, I^2 3.2%) after transfusion of fresh platelets. The weighted mean difference in the observational studies was 0.07 units (CI -0.06 to 0.25), and this was 2.50 units (CI -1.23 to 6.23) in the randomized trial (supplemental material).
Two papers (two comparisons) were included in the meta-analysis of need of plasma transfusions. The weighted mean difference was 0.09 products fewer (95% CI: -0.06 to 0.25, I^2 0.0%) after transfusion of fresh platelets (figure 3). One study reported the need of cryoprecipitate, which was not different after transfusion of fresh or old platelets (table 1).

Other efficacy outcomes
One randomized trial and one cohort study reported an increased risk of a repeated transfusion within 24 hours (table 1). Results from these studies could not be pooled as the storage time of the old platelets in one paper coincided with the storage time of the fresh platelets in the other.
One study determined the hemostatic potential of platelets using thromboelastography (TEG) and reported better hemostatic properties of fresh platelets compared to old platelets (table 1).

Figure 3. Forest plot of studies reporting efficacy outcomes and storage time



A. Forest plot of studies comparing the interval between subsequent platelet transfusion in days. The numbers represent the weighted mean difference (WMD), calculated as: 'interval fresh' – 'interval old'.
B. Forest plot of studies reporting the risk of bleeding. The numbers represent the relative risk of old platelets compared to fresh platelets with corresponding 95% confidence interval for each study.
C. Forest plot of studies reporting transfusion need. The numbers represent the weighted mean difference, calculated as 'number of products old' – 'number of products fresh'.
** Product codes: Aph = apheresis, BC-PAS = buffy coat stored in PAS, BC-plasma = buffy coat stored in plasma, PR = pathogen-reduced.*
† Results shown for all studies. Selecting only studies in hematological patients yields a weighted mean difference of 4.51 units (CI 1.92; 7.11).

Discussion

To conclude, transfusion of older platelet products was associated with more transfusion reactions before the implementation of universal leukoreduction. This association disappeared after the implementation of universal prestorage leukoreduction. Transfusion of older platelet products was associated with a shorter time to the next transfusion, a trend towards a higher risk of bleeding, and in hematogical patients an increased need of platelet transfusions. Storage time of

platelet concentrates was not associated with the risk of mortality nor the consumption of other blood products.

The association between storage time and laboratory measurements (i.e. platelet counts and derivatives thereof) has been reported elsewhere. That study reported inferior results for older platelets for all relevant measurements.[8] The current results suggest that these lower laboratory values are associated with a higher risk of bleeding and a shorter time to the next transfusion. Decreased efficacy of old platelets could explain the increased bleeding risk. Another explanation could be that platelet count is routinely measured on fixed moments, e.g. three times a week. Transfusion of older platelets results in lower increments, leading to a lower platelet count on average in case of a prophylactic transfusion strategy. This could result in an increased bleeding risk.
The increased risk of transfusion reactions in old platelets could be attributed completely to studies performed before the implementation of pre-storage leukoreduction. Leukocytes and leukocyte-derived cytokines are thought to be a major cause of febrile non hemolytic transfusion reactions.[25,26]
With the implementation of universal leukoreduction an absolute risk reduction of 25.1% was expected in the risk of febrile non hemolytic transfusion reactions.[27] The results of the present meta-analyses confirm the beneficial effect of pre-storage leukoreduction on the incidence of transfusion reactions.

An important strength of these meta-analyses is that we were able to pool the available data on bleeding risk. Most studies are powered to study other outcomes and are therefore by themselves inconclusive on bleeding risk. Although different definitions of bleeding are used, we assume storage time has the same effect on all symptoms and it is appropriate to pool the estimates.
Another strength of this study is the broad search strategy. No limits were used for study design, year or language. Therefore, a maximum of available papers reporting clinical effects of storage time have been retrieved and all reported clinical outcomes were studied.
The broad search strategy also returned meeting abstracts, which are possibly more prone to bias. Exclusion of the meeting abstracts did not change the results of the main analyses, indicating these abstracts estimate the same effect. Due to the limited number of randomized trials it was not feasible to perform a sensitivity analysis including only randomized trials. However, the pooled estimates of the observational studies were comparable with the results of the randomized trials. This suggests that the observational studies are reliable, allowing inclusion in the

meta-analysis. The relatively large difference between the estimates of the observational studies and the randomized trials in transfusion interval is based on one precise observational study in which the difference in interval was 0.19 days (CI 0.13 to 0.24).

The main limitation of this study is that storage time had to be dichotomized into two broadly defined categories, fresh and old. Most studies reported differences between two groups and defined fresh as storage time of ≤3 days. Therefore it was impossible to compare the safety and efficacy of platelets stored for 1-5 days with platelets stored for 6-7 days. Whereas this is the difference between storage duration used in the Netherlands, compared with several other countries.[2-5]
Not all retrieved studies could be included in the meta-analyses, which could potentially induce selection bias. However, the studies excluded from the meta-analysis regarding transfusion interval, reported on average a similar interval as the pooled estimate of the meta-analysis and for the outcomes transfusion reactions and bleeding, the results of the excluded studies pointed in the same direction.

Another limitation of this study is the large heterogeneity between studies reporting transfusion reactions (I^2 83.1%). This is partly due to the difference in effect observed before and after the implementation of universal leukoreduction. Correction for leukoreduction in metaregression explained 42% of this heterogeneity. Other sources of variation could include the lack of standardized definitions and differences between active and passive monitoring of transfusion reactions. Among studies reporting bleeding symptoms heterogeneity was moderate. This could be due to the fact that several different definitions of bleeding are used and it is measured in different ways. The number of studies reporting on the other outcomes was smaller and therefore it is difficult to detect heterogeneity and publication bias for these outcomes.

In conclusion, the safety and efficacy of platelet products deteriorates during storage. However, leukoreduction reduces the risk of transfusion reactions following transfusion of old platelets effectively. Efficacy of platelet transfusions is reduced after prolonged storage, leading to a shorter interval to the next platelet transfusion. Transfusion of old platelet concentrates might increase the risk of bleeding.

Supplemental material

Available at
http://onlinelibrary.wiley.com/doi/10.1111/vox.12494/abstract#footer-support-info

Data S1. Search queries.
Table S1. Overview of all included comparisons per product.
Figure S1. Funnel plot of studies comparing incidences of transfusion reactions.
Figure S2. Funnel plot of efficacy of platelet transfusion.
Figure S3. Sensitivity analysis: forest plot transfusion reaction, bleeding and platelet storage time.
Figure S4.Sensitivity analysis: forest plot safety outcomes, excluding the randomized trials.
Figure S5. Sensitivity analysis: forest plot efficacy outcomes, excluding the randomized trials.
Figure S6. Forest plot transfusion interval and transfusion need and platelet storage time, standardized analysis.

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