Chapter 5

Effect of platelet storage time on platelet measurements: a systematic review and meta-analyses

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Abstract

Background

The storage time of platelet products negatively affects bacterial safety and platelet function. However, low maximum storage time increases outdating of valuable products. Thus, to quantify the effect of platelet storage time on platelets measurements after platelet transfusion a systematic review and meta-analyses were performed.

Methods

Reports and meeting abstracts of randomized trials and observational studies, performed in humans, reporting platelets measurements after transfusion of platelet products of different storage times were selected until February 2016. Meta-analyses were performed for four different storage time contrasts, each answering a different question. Random effects models were used to account for substantial heterogeneity and the weighted mean differences were calculated.

Results

Our search strategy yielded 4,234 studies of which 46 papers satisfied the inclusion criteria. As judged by the 1 hour corrected count increment, transfusion of fresher platelets compared to stored platelets showed better increment. The weighed mean difference varied from 2.11 (95%CI: 1.51 to 2.71) to 2.68 (95%CI: 1.92 to 3.45). For the 24 hour corrected count increment the weighted mean difference varied from 1.36 (95%CI: 0.12 to 2.60) to 1.68 (95%CI: 1.07 to 2.28) depending on the contrast. Recovery and survival of old platelets as percentage of fresh platelets were 81% and 73% for the original definition contrast. For the extended storage contrast recovery and survival were 75% and 68%.

Conclusions

Fresh platelets were superior to old platelets for all platelets measurements and for all storage time contrasts meta-analyzed.

Introduction

Many papers have been published relating storage time of blood products to clinical outcomes and measurements. However, most of these focus on red blood cells.[1-9] Platelets are essential for hemostasis. Patients with thrombocytopenia or thrombocytopathy, due to hematologic malignancies, other blood disorders, bleeding, or medication, require platelet transfusions to prevent or treat bleeding.[6,7] The storage time of platelet products negatively affects bacterial safety and platelet function.[8,9] However, low maximum storage time increases outdating of valuable products. The balance between avoiding wastage and maintaining product safety and quality determines optimal storage time.[10] Maximum storage of platelets can be three to seven days, depending on the local or national guidelines and the type of product. For example, maximum storage time is three days in Japan[11], four days in Germany[12], and five days in the United States[13] and Brazil.[14] In The Netherlands, platelet products can be stored for a maximum of seven days.[15] As blood banks world-wide seek to increase maximum storage times, seven days storage will become more common. The effect that seven days storage has on product quality and safety will therefore become ever more important. In 2014 the Food and Drug Administration issued a draft guidance on safety testing and, during their 2015 annual meeting, the American Association of Blood Banks hosted a dedicated session "Paving the Way Towards Implementation of 7 Day Platelets". Several studies have investigated the effect of storage time of platelets on platelets measurements and other outcomes.[16,17] However, no comprehensive systematic summary and quantification (meta-analyses) of the available evidence has been made to date. The objective of this systematic review and meta-analyses was to quantify the effect of platelet storage time on platelets measurements after platelet transfusion.

Methods

Search strategy

As pre-specified in the study protocol (supplemental material, appendix 1), we performed a systematic review to identify all randomized clinical trials and observational studies reporting storage time of platelets products. Potentially relevant papers and meeting abstracts were identified using MEDLINE (PubMed), EMBASE, Cochrane, CINAHL, Academic Search Premier, ScienceDirect and Web of Science databases until February 2016. No restriction on study design, language or year of publication was used (supplemental material appendix 2). Non-English papers were translated by native (Chinese and German) or fluent (Russian) speakers.

Study selection

Two reviewers independently reviewed, titles and abstracts to select studies reporting platelets storage time and platelets measurements. Pre-specified inclusion criteria were: (i) human: papers reporting exclusively animal studies were excluded; (ii) platelet product transfusion: papers that were exclusively about other blood products or about endogenously produced platelets were excluded; (iii) clinical (performed in patients or volunteers): in vitro, ex vivo, laboratory experiments, and simulation studies were excluded; (iv) storage time: reported as a variable in the paper; (v) original: letters, comments, and reviews not containing any original data were excluded; (vi) platelets measurements: papers that reported at least one of the five platelets measurements (count increment [$\times 10^9$/L]: pre-transfusion platelet count subtracted from post-transfusion platelet count;[16] corrected count increment [/dm]: count increment corrected for body surface area and platelet product dose;[16] recovery: proportion of platelets recovered from the circulation;[17] survival: mean residual life span;[17] and half-life) and (vii) data necessary for meta-analyses reported: point estimate (i.e. mean or median) and measure of precision (i.e. standard deviation, standard error, interquartile range or range).

Disagreements between reviewers were discussed with a third reviewer. Papers were included for full text assessment if no decision was possible on title and abstract alone.

Full text papers were reviewed again for all inclusion criteria. Papers were excluded if the data presented were the same (totally or partially) as those presented in another selected paper. In this case papers were preferred over meeting abstracts and chronologically newer papers were preferred over older ones.

Risk of bias assessment

The risk of bias was evaluated using “The Cochrane Collaboration’s tool for assessing risk of bias” to evaluate randomized clinical trials, and the “Fowkes & Fulton tool” to evaluate both randomized clinical trials and observational studies.18-20 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 are similar to the ACROBAT NRSI Cochrane tool for assessing non-randomized studies.[21] For the randomized studies there was perfect agreement between the two tools. Papers with high risk of bias in any of the assessed domains of bias were excluded from the final selection.

Storage time definition

For simplicity only the terms 'fresh' and 'old' are used throughout this paper. The term 'fresh' is used to refer to the storage time group stored for a shorter time than its comparator group (in the same paper). Common synonyms for 'fresh' used in the literature include 'new' and 'young'. The term 'old' is used to refer to the storage time group with the longer storage time. Common synonyms for 'old' include 'stored' and 'aged'.

Storage time comparisons

To answer different questions regarding the effect of storage time of platelets results were meta-analyzed in four different ways.[22] If a paper did not report the results in a way compatible with dichotomizing the data according to one of these definitions, that paper was excluded from that particular analysis.

a) Original definition (as reported): Fresh and old were included in the meta-analysis as reported in the paper. If a paper's results were not presented in two groups the results were dichotomized into fresh if stored ≤3 days and old if stored ≥4 days.
b) Maximum storage 5 days (0-2 vs. 3-5): Papers were included that reported results for zero to two days (fresh) and three to five days (old). This analysis provides a clinically relevant answer to the question whether platelets on the 'fresh half' of the storage time spectrum are different from those on the 'old half', for the very common situation where the maximum storage time is five days
c) Extreme difference (0-2 vs. 5-7): To examine the effect of extreme differences in storage time only papers were included if they reported results for zero to two days (fresh) and five to seven days (old). This analysis provides the strongest contrast and therefore is the most sensitive indication whether any effect exists or not.
d) Extended storage (0-5 vs. 6-7): In this analysis papers were included that reported results for zero to five days (fresh) and for six or seven days (old). This analysis compares 'standard maximum storage' of five days directly to 'extended storage' till seven days. It is therefore most relevant to the situation where extended storage is either allowed, or under consideration for implementation.

Each one of these four meta-analyses was performed independently. For all analyses a minimum of five papers (per platelets measurement) was required to estimate the pooled effect. Clinical measurements reported in less than five papers

were reported in the selection flowchart (figure 1), but were not included in the meta-analyses. Moreover, for all analyses, results from storage time beyond normal blood banking practice (i.e. >7 days) were disregarded. Pooled effects are presented per platelets measurement.

Data extraction

As specified in the study protocol (online appendix 1), all relevant data reported in the papers were first recorded exactly as reported and subsequently organized and recalculated as described below. Products were grouped into four product groups: apheresis platelets stored in plasma (apheresis plasma), buffy-coat derived platelets stored in plasma (BC plasma), platelet rich plasma (PRP), and buffy-coat derived platelets stored in platelet additive solution (BC PAS). To allow pooling of the data, the original results sometimes needed to be recalculated or transformed:

a) If the standard error of the mean (SEM) was reported, the standard deviation (SD) was calculated: $SD = SEM * \sqrt{n}$;
b) Mean and standard deviation were calculated from medians, ranges and quartiles,[23] since a normal distribution could be expected to be the true underlying distribution from which sampling took place. Only six out of 46 studies did not report their results as normally distributed. We therefore assumed those six were not sufficiently confident of a normal distribution based on their own results alone. Based on the other 40 studies, all sampling from the same underlying distribution, and all reporting a normal distribution, we could be more confident than any individual study;
c) Similar products (i.e. differences in post-production processing) were merged using standard formulas for combining samples sizes (Σn_i), means ($\sum \overline{x_i} * n_i / (\sum n_i)$) and standard deviations ($SD = (\Sigma(n_i - 1)s_i^2 / \Sigma(n_i - 1))^{½}$) from multiple groups. Whereas really different products (i.e. different donation procedure or storage medium) presented in the same paper were not merged;
d) When necessary originally reported categories were merged into the four different definitions of fresh versus old using standard formulas, as described above (item c);
e) Results presented in hours were recalculated to days;
f) Platelets measurements reported between zero and four hours after transfusion were considered ‘1 hour’; platelets measurements reported between eight and 28 hours after transfusion were considered ‘24 hours’.

Analyses

Results were pooled across studies using random effects methods to account for substantial heterogeneity, as indicated by high I^2-values. Weighted mean differences, also known as non-standardized mean differences, were calculated for continuous outcomes. Heterogeneity between studies was assessed using the I^2 statistic. The I^2 value ranges from 0% to 100% and calculates the proportion of variation due to heterogeneity rather than due to chance. Reporting (or publication) bias was analyzed using a funnel plot and its asymmetry was assessed using Egger's test.[24] All outcomes (i.e. parameters) were transformed to the same scale to allow the construction of a single funnel plot for all platelets measurements combined. The standardized model was therefore used in this analysis (i.e. as opposed to the non-standardized model used to report the main effects) and all studies were centered around the null effect by subtracting the standardized mean differences per platelets measurement.

Recovery and survival were expressed as percentage recovery and survival achieved with old platelets, compared to fresh platelets. This provides some insight into the order of magnitude of difference to expect, since it allows comparison to the requirements of the Food and Drug Administration (FDA). The FDA requires a minimum of 67% for recovery and 58% for survival, compared to day zero platelets, for any type of platelet product or production process to be allowed into platelets use.[13]

Additional analyses

Additional analyses were performed to clarify whether observed heterogeneity could potentially be attributed to effect modification. Explored possible underlying differences included differences in outcomes, storage times contrasts (analyses a to d), product types, studies populations, and studies design: (i) funnel plot for each outcome separately; (ii) forest plots for each outcome separately and stratified by different product types and different populations; and (iii) summary mean difference according to whether the study was randomized or not.

Results

Selection

The search retrieved 4,234 records. 4,099 records were excluded because they were: an exclusively animal study (199); not about platelet transfusions (1521); not *in vivo* or did not report a platelets outcome (1077); not about storage time (234); did not present original data (196); or because the titles were irrelevant (872 from

the 886 records which abstracts were not available). Upon full text review of the remaining 135 papers a further 48 were excluded because of the above mentioned exclusion criteria (n=32), or because of high risk of bias (n=16, mostly because the fresh and old groups also differed in other respects like storage medium, type of storage bag, storage conditions, type of donation, or production process). Further nine papers were excluded because their data were presented in another selected paper, 19 because they did not report any platelets measurement and 13 because they did not report the data necessary for the meta-analyses. The final selection included 46 papers, 13 randomized trials and 33 observational studies (figure 1). The complete list of selected papers and their qualitative overview can be found in the supplemental material (appendix 3). Only six papers failed to report normally distributed results. To allow pooling the data their results were recalculated (see methods section for details).

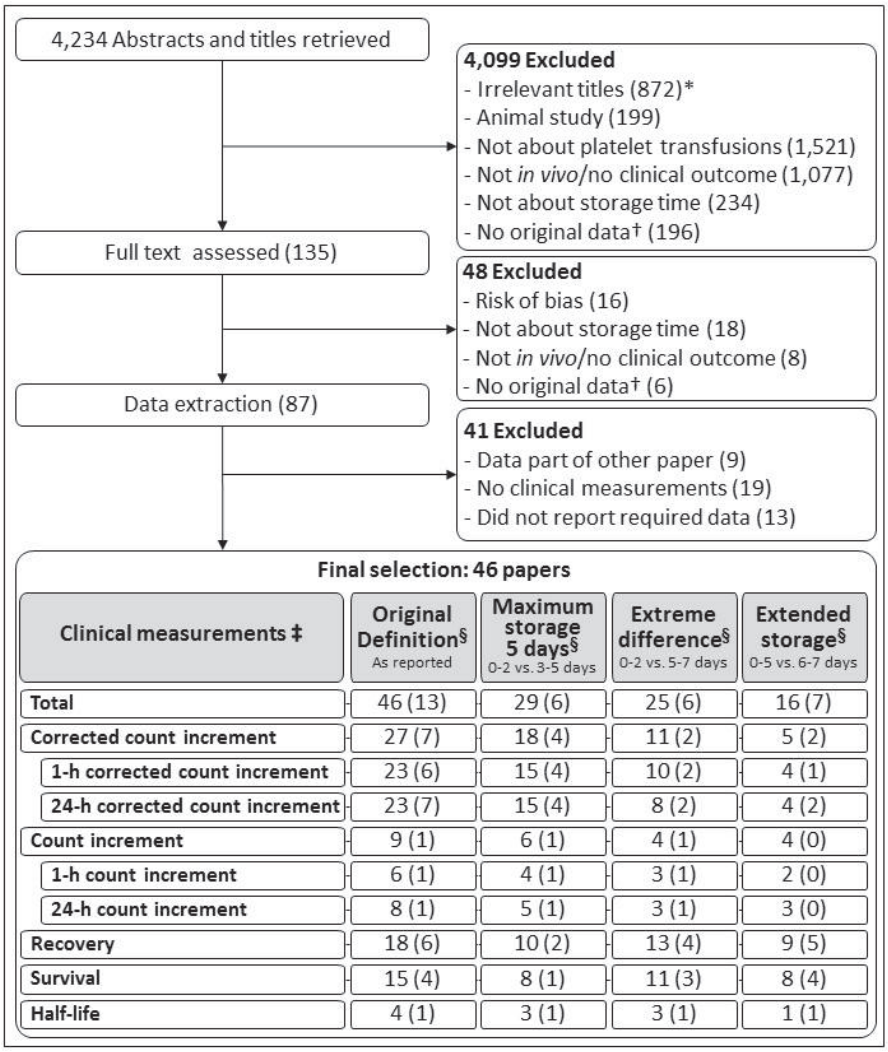
Reported outcomes

Of the 46 selected papers, 27 papers reported corrected count increments (23 reported the 1 hour and 23 reported the 24 hour corrected count increment). Nine papers reported count increment (six papers reported 1 hour and eight reported 24 hour count increment). Eighteen papers reported platelet recovery. Survival was reported in 15 papers and half-life was reported in four (figure 1).

Meta-analyses

Figure 2 shows the funnel plot for all outcomes combined. There is a relative lack of smaller studies (i.e. larger standard error) favoring older platelets, compared to either smaller studies favoring fresh platelets or larger studies. This indicates a bias towards withholding publication of small and therefore statistically unreliable studies showing a benefit of older platelets. Publication bias was present as indicated by Egger's bias coefficient 2.14 (95% confidence interval (CI): 1.59 to 2.70). Half-life did not reach the cut-off of a minimum of five papers and was therefore not included in any of the meta-analyses.

Figure 1. Flowchart study selection



Clinical measurements ‡	Original Definition§ As reported	Maximum storage 5 days§ 0-2 vs. 3-5 days	Extreme difference§ 0-2 vs. 5-7 days	Extended storage§ 0-5 vs. 6-7 days
Total	46 (13)	29 (6)	25 (6)	16 (7)
Corrected count increment	27 (7)	18 (4)	11 (2)	5 (2)
1-h corrected count increment	23 (6)	15 (4)	10 (2)	4 (1)
24-h corrected count increment	23 (7)	15 (4)	8 (2)	4 (2)
Count increment	9 (1)	6 (1)	4 (1)	4 (0)
1-h count increment	6 (1)	4 (1)	3 (1)	2 (0)
24-h count increment	8 (1)	5 (1)	3 (1)	3 (0)
Recovery	18 (6)	10 (2)	13 (4)	9 (5)
Survival	15 (4)	8 (1)	11 (3)	8 (4)
Half-life	4 (1)	3 (1)	3 (1)	1 (1)

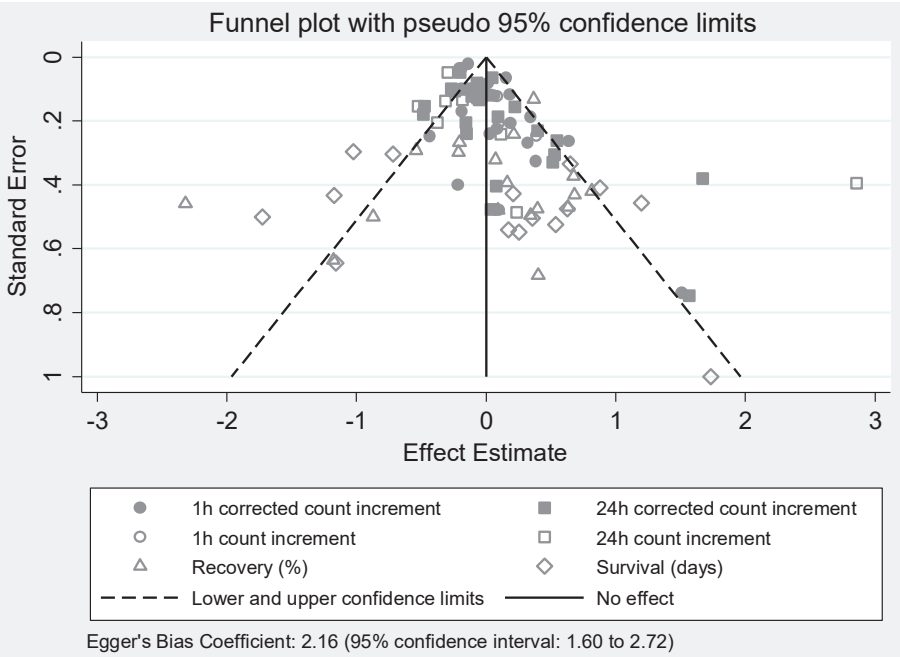
** 886 titles screened (abstracts not available);*

† letters/comments/reviews/reports;

‡ more than one possible outcome per paper

§ between brackets the number of 'randomized trials'

Figure 2. Funnel plot



a) Meta-analysis: original definition (as reported)

Figure 3a shows the pooled weighted mean differences of fresh platelets minus old platelets. Pooled effect estimates were: 1 hour corrected count increment 2.30 (CI: 1.72 to 2.88); 24 hour corrected count increment 1.68 (CI: 1.07 to 2.28); 1 hour count increment 4.47 (CI: 2.13 to 6.82); 24 hour count increment 4.60 (CI: 0.73 to 8.47); recovery 11.12% (CI: 7.80% to 14.43%); survival 2.08 days (CI: 1.63 to 2.52). The I^2 ranged from 53% to 92% (table 1 and figure 3a). Based on the pooled means and standard deviation, recovery of old platelets was 81% of fresh platelets and survival of old platelets was 73% of fresh platelets (table 1).

b) Meta-analysis: maximum storage 5 days (0-2 vs. 3-5 days)

Twenty-nine papers were included in this analysis, 18 papers reported corrected count increment (15 the 1 hour corrected count increment, and 15 the 24 hour corrected count increment) and six reported count increment (four the 1 hour count increment, and five the 24 hour count increment). Recovery and survival were reported in ten and eight papers.
The pooled weighted mean differences estimated for fresh minus old were: 1 hour

corrected count increment 2.11 (CI: 1.51 to 2.71); 24 hour corrected count increment 1.36 (CI: 0.12 to 2.60); 24 hour count increment 4.69 (CI: 0.41 to 8.96); recovery 7.41% (CI: 1.53% to 13.28%) and survival 1.59 days (CI: 1.01 to 2.17). I^2 ranged from 45% to 90% (table 1 and figure 3b). Recovery and survival of old platelets were 88% and 80% of fresh platelets (table 1).

c) Meta-analysis: extreme difference (0-2 vs. 5-7 days)

Twenty-five papers were included in the extreme difference (0-2 vs. 5-7 days) meta-analyses. Ten papers reported corrected count increment as an outcome (11 the 1 hour corrected count increment and eight the 24 hour corrected count increment). Four papers reported count increment (three the 1 hour count increment and three the 24 hour count increment). Recovery, and survival were reported in 13 and 11 papers (figure 1).

Figure 3c shows the pooled weighted mean differences for fresh minus old for corrected count increment, recovery and survival. Count increment did not reach the cut-off of a minimum of five papers. Pooled effect estimates were: 1 hour corrected count increment 2.68 (CI: 1.92 to 3.45); 24 hour corrected count increment 1.36 (CI: 0.08 to 2.63); recovery 12.71% (CI: 7.63% to 17.80%); and survival 2.30 days (CI: 1.76 to 2.84). The I^2 ranged from 46% to 81% (table 1 and figure 3c). Recovery of old platelets was 80% of fresh and survival was 71% (table 1).

d) Meta-analysis: extended storage (0-5 vs. 6-7 days)

Sixteen papers compared standard storage (0-5 days) to extended storage (6-7 days). Nine papers reported recovery and eight papers reported survival as an outcome. Corrected count increment and count increment did not reach the cut-off of a minimum of five papers. The pooled weighted mean differences for fresh minus old were: recovery 15.44% (CI: 10.22% to 20.66%) and survival 2.48 days (CI: 1.86 to 3.09). The I^2 were 70% and 72% (table 1 and figure 3d). Recovery and survival of old platelets were 75% and 68% of fresh platelets (table 1).

Table 1. Mean differences in platelets measurements after transfusion of fresh and old platelets products according to four different definitions of fresh and old.

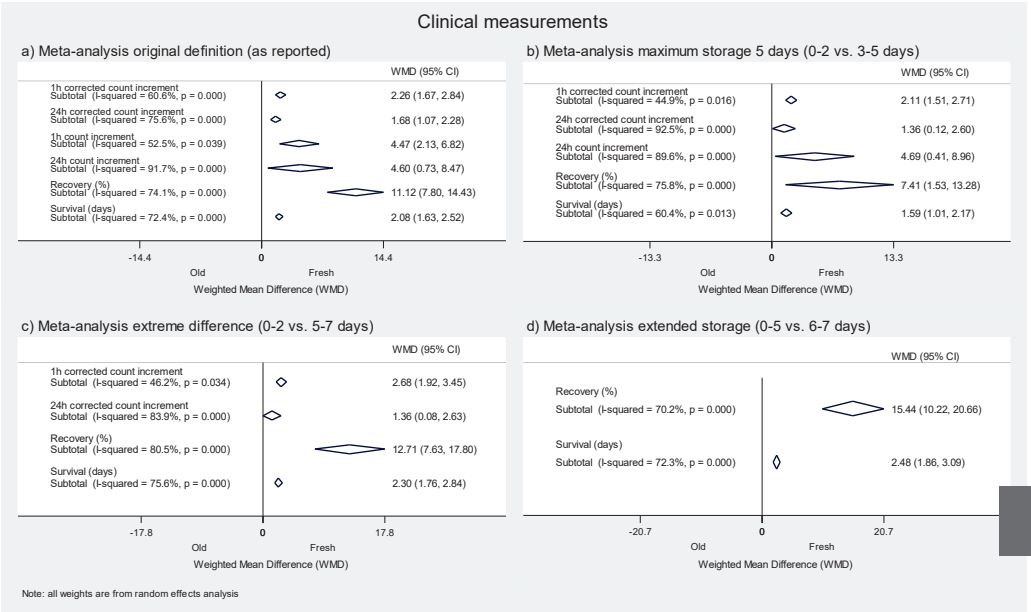
	Original definition as reported	**Maximum storage 5 days 0-2 vs. 3-5 days**	**Extreme difference 0-2 vs. 5-7 days**	**Extended storage 0-5 vs. 6-7 days**
1h corrected count increment	2.30 (1.72 to 2.88)	2.11 (1.51 to 2.71)	2.68 (1.92 to 3.45)	-
24h corrected count increment	1.68 (1.07 to 2.28)	1.36 (0.12 to 2.60)	1.36 (0.08 to 2.63)	-
1h count increment	4.47 (2.13 to 6.82)	-	-	-
24h count increment	4.60 (0.73 to 8.47)	4.69 (0.41 to 8.96)	-	-
Recovery (%)	11.12 (7.80 to 14.43)	7.41 (1.53 to 13.28)	12.71 (7.63 to 17.80)	15.44 (10.22 to 20.66)
old as % of fresh*	81%	88%	80%	75%
Survival (days)	2.08 (1.63 to 2.52)	1·59 (1.01 to 2.17)	2.30 (1.76 to 2.84)	2.48 (1.86 to 3.09)
old as % of fresh*	73%	80%	71%	68%

Values are weighted mean differences fresh minus old (95% confidence interval) or percentages (%)
**old as percentage of fresh*

Additional analyses

The supplemental material shows funnel plot for each outcome separately and complete forest plots for each outcome separately, stratified by different product types and different populations. It also presents summary mean difference according to whether the study was randomized or not and the underlying distribution (absolute numbers) of the weighted mean differences (appendix 4 and 5). All results were similar to the overall pooled results as presented in the main text, table, and figures.

Figure 3. Summary mean differences between fresh and old platelet products in platelet measurements according to four different definitions of old and fresh.



Heterogeneity, as indicated by I^2 values, was typically much lower in analyzed subgroups, especially upon stratification by product type. This indicates product type to be a source of heterogeneity. However, since overall pooled results were very similar to pooled subgroup results, overall results can be used as summary measures. Subgroup results are therefore only reported in the supplemental material, appendix 4.

Discussion

Fresher platelets were superior to older platelets for all platelets measurements and all different storage time contrasts investigated. Strengths of this study include the comprehensiveness. There were no limitations on the type of outcome, publication date, study design, population, and language. Also, search keywords were defined very broadly, including as many papers as possible. The search strategy was applied to many different literature databases and queries for all databases were built by a senior librarian, specialized in performing systematic literature searches. This approach likely ensured that all potentially relevant papers were retrieved.

From all selected papers the maximum possible amount of available data were retrieved. Data reported in ways that did not allow pooling (e.g. medians and ranges or interquartile ranges), were recalculated into means and standard deviations, which do allow pooling. Data were extracted from graphs when necessary. Therefore, we were able to pool the results and perform the meta-analyses on data from as many papers as possible.

Another important strength of this study is the quality of included data. Risk of bias was assessed in two different ways and we found perfect agreement between the two assessment tools. Out of 135 studies reporting at least one platelets measurement 16 were excluded based on the risk of bias assessment. Of the remaining studies data that allowed for pooling of results in the meta-analyses could be extracted from 46.

A possible limitation is that not enough randomized trials were included to perform a meta-analysis restricted to randomized trials. However, to have full transparency of our reporting, we showed results stratified between randomized trials and non-randomized trials in the supplemental material. All results in these analyses were in the same direction and in the same magnitude as those presented in the main text.

Another remark to be made is about the high heterogeneity between the studies measured as I^2. As recommended by The Cochrane, besides verifying the data and exploring the heterogeneity, a random-effects meta-analysis was performed.[25]

We found indications of the presence of publication bias. The funnel plot shows a slight preference for smaller studies favoring fresher platelets and Egger's bias coefficient also indicates the presence of publication bias. However, the funnel plot is centered around zero by subtracting the standardized mean effect. Therefore, the largest observed ‘negative effect’, is in reality still an effect in favor of fresher platelets. Thus, although publication bias may have had a minor effect on the size of our effect estimates, it seems unlikely that this could have materially influenced our conclusions.

These potential consequences of transfusing older platelets, however, have to be put in perspective relative to the consequences of supplying exclusively fresher platelets. The Dutch blood supply organization (Sanquin) switched to extended storage of platelets (i.e. maximum storage of seven days instead of five) in 2002. This prolongation of storage time reduced outdating from 20% to about 10%, reducing cost and increasing platelet availability.[26]

In conclusion, our results indicate that fresh platelets are more likely to result in a successful transfusion than old platelets. With successful transfusion defined as a count increment based measurement being above a specific threshold. However, as currently judged by means of a corrected count increment, the success of a transfusion results from a mixing of effects of patient and product related factors. To be clinically relevant the judgment of success of a transfusion should depend on patient related factors only and be separated from product related factors as much as possible. So besides body surface area and platelet dose of the product, storage time should also be taken into account, to arrive at an even better corrected count increment to judge the success of transfusions. We therefore recommend more research into a storage time independent measure for the success of a platelet transfusion.

Supplemental material

Available at http://onlinelibrary.wiley.com/doi/10.1111/vox.12443/full#footer-support-info

Appendix S1. Protocol
Appendix S2. Search strategy: queries
Appendix S3. Reference list and qualitative overview – Included papers
Appendix S4. Funnel plot per outcome; forest plots of weighted mean differences per outcome, product group and population (patients/volunteers); and Summary mean differences according to study design (RCT/Non-RCT)
Appendix S5. Underlying distributions (absolute numbers) of the weighted mean differences

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