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

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CHAPTER 6

Storage time of platelet concentrates and the diagnosis of platelet refractoriness

Submitted

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ABSTRACT

Background: Haemato-oncology patients undergoing intensive chemotherapeutic treatments receive prophylactic platelet transfusions. Differences in count increments after transfusion of fresh or old platelets have been reported, but are difficult to translate directly into real clinical success of a transfusion. However, lower increments are used to label transfusions as "failed" and diagnose platelet transfusion refractoriness. Therefore, we now quantified the association of storage time with the expected percentage of failed transfusions, for a range of possible count increment thresholds, to estimate the number of unnecessary diagnoses of refractoriness.

Methods: Based on results from a meta-analysis, the expected percentages of failed and successful transfusions were estimated for two different definitions of fresh and old transfusions.

Results: For the 'Maximum storage 5 days' contrast (0-2 versus 3-5 days), based on the 24 hour absolute count increment, for thresholds ranging from 0 to 30, the difference in the percentages of failure, between old and fresh transfusions, ranged from 4.9% to 5.5%. Based on the 1 hour corrected count increment, for thresholds ranging from 0 to 15, the differences between old and fresh transfusions, ranged from 2.7% to 10.4%. After 24 hours these differences ranged from 4.3% to 6.2%.

Conclusion: Out of every 20 old platelet transfusions one will be considered failed, while a fresh platelet transfusion would have been successful. This will happen, irrespective of any patient characteristics or clinical factors. This failure is therefore likely to have limited clinical relevance and could result in an unnecessary diagnosis of refractoriness.

INTRODUCTION

Prophylactic platelet transfusions are an important supportive therapy for haemato-oncology patients undergoing intensive chemo-therapeutic treatments.[1] We recently performed a systematic review and meta-analyses, quantifying the association of platelet storage time and absolute and corrected count increments.[2] Our results confirmed the expected difference in count increments between fresh and old platelets. The observed difference in 1 hour corrected count increment was 2.11 (95% confidence interval (CI): 1.51 to 2.71) between fresh and old platelets. The difference in the 24 hour corrected count increment was 1.36 (CI: 0.12 to 2.60).[2] However, directly translating these differences into a clinically relevant interpretation is difficult. Especially since the relevance of platelet counts and count increments for the haemostatic effect, which is the true measure of success of a platelet transfusion, might be limited.[3-5]

One way in which a difference in count increment might become clinically relevant, completely independently of any potential effect on haemostasis, is by its influence on the diagnosis of refractoriness. What is mostly agreed upon is that a patient is to be considered refractory to platelet transfusion if he or she fails to show adequate increments in platelet count on at least two consecutive platelet transfusions.[1,6-11] Formally, these two consecutive transfusions are supposed to be both with fresh platelets (i.e. <72 hours of storage).[9,10] However, in clinical practice it is not possible to specifically order two consecutive transfusions of fresh platelets for all patients. Additionally, a blood bank supplying predominantly older platelets is likely to supply two consecutive old transfusions and a blood bank supplying predominantly fresh platelets is likely to supply two consecutive fresh transfusions. By basing the diagnosis of refractoriness on the perceived failure of two consecutive transfusions, while failure is defined based on count increments and count increments are known to depend on storage time, patients will be deemed refractory, while the storage time of the transfused product was really to blame. In these patients diagnostic work-up for suspected refractoriness will be started unnecessarily.

For the diagnosis of refractoriness the percentage of successful transfusions is more directly relevant than the observed absolute or corrected count increment. However, what constitutes a 'successful' or a 'failed' transfusion, based on count increments, is difficult to define exactly.[6,7,9] Different thresholds for what should be considered adequate count increments and corrected count increments have been suggested.[1,6,12] Some clinicians more informally consider a transfusion 'failed' if another one is needed the next day (i.e. no or clinically irrelevant 24 hour absolute count increment). Others calculate corrected count increments and strictly adhere to a certain pre-specified threshold for success of a transfusion. The exact definition chosen to determine the "success of a transfusion", based on platelet count derived measures, could affect the relative size of the effect of storage time on the percentage of successful transfusions and therefore on the number of unnecessary diagnoses of refractoriness.

Therefore, we now further investigated the previously reported count increments, to quantify the association of storage time with the expected percentage of failed transfusions, for a range of possible absolute and corrected count increment thresholds, to estimate the number of unnecessary diagnoses of refractoriness expected.

METHODS

We previously performed a systematic review and meta-analyses, including any publication indexed in MEDLINE (PubMed), EMBASE, Cochrane, CINAHL, Academic Search Premier, ScienceDirect and Web of Science databases, until February 2016, about the direct comparison of fresh versus old platelet transfusions and their effect on clinical measurements (i.e. platelet counts and derived measures) after transfusion. The terms 'fresh' and 'old' were analysed in different ways as described previously.[2] For the current analyses we selected two storage time contrasts to increase homogeneity in the definition of fresh and old platelets:

- **Maximum storage 5 days (0-2 versus 3-5 days):** Papers were included that reported results for zero to two days (fresh) and three to five days (old).
- **Extreme difference (0-2 versus 5-7 days):** Papers were included that reported results for zero to two days (fresh) and five to seven days (old).

The expected percentages of successful transfusions were estimated for the 1 hour and the 24 hour absolute and corrected count increments, for old and fresh transfusions. All reported absolute correct increment are expressed in [$\times 10^9$/l] and correct count increments are expressed in [/dm]. The percentages of success were derived from the normal distributions for these outcomes as estimated based on the weighted mean differences and standard deviations from the random effects models from the previously published meta-analyses[2] (for formulas see online supplemental material). Figure 1 shows the distributions of count increments for fresh and old transfusions. For each fixed threshold (x) the left area under the curve represents the percentage of failed transfusions and the right area represents the percentage of successful transfusions. The grey area represents the increase in the percentage of failed transfusions among transfusions of old platelets, compared to transfusions of fresh platelets.

Thresholds (x) for 'successful' or 'failed' transfusions varied from 0 to 30 for absolute count increments and from 0 to 15 for corrected count increments. Number need to tread (NNT) were calculated using the following formula:

$$NNT = \frac{1}{Absolute\ risk\ difference} =$$

$$= \frac{1}{P_{failure}(old) - P_{failure}(fresh)}$$

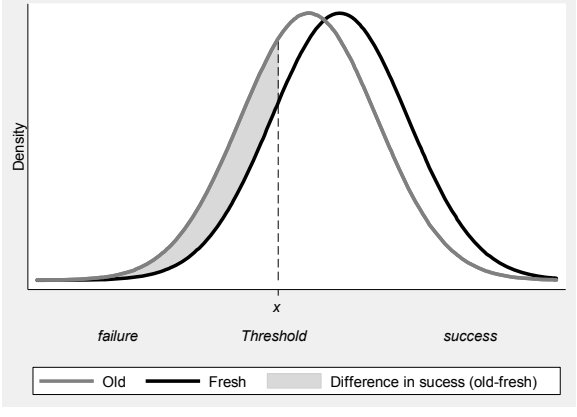

Figure 1: Distribution of platelet count increments

The area to the left of threshold represents failure and the area to the right of the threshold represents success. Grey area represents the difference between old and fresh distributions at the threshold x

RESULTS

Of the 46 papers selected in the original meta-analyses, 29 reported absolute or corrected count increments. The data of these 29 papers were used to estimate the distributions count increments and corrected count increments for fresh and old platelets and the percentages of 'successful' or 'failed' transfusions. Nine papers reported count increments: six papers reported 1 hour count increments of 4,822 transfusions, and eight reported 24 hour count increments of 3,531 transfusions. Twenty-seven papers reported corrected count increments: 23 reported the 1 hour corrected count increments of 19,117 platelet transfusions, and 23 reported the 24 hour corrected count increments of 8,032 platelet transfusions (Table 1).

Table 1 also shows the mean increment of old and fresh platelets and the combined standard deviations for each definition of old and fresh. Fresh platelets had higher mean absolute and corrected count increments than old platelets for all the contrasts studied.

Absolute Count increment

For the 'Maximum storage 5 days' contrast (0-2 versus 3-5 days), for thresholds ranging from 0 to 30 L, based on the 24 hour increment, the percentages of failed transfusions ranged from 32% to 66% for fresh platelets and from 37% to 71% for old platelets. This corresponded to differences, between old and fresh transfusions, ranging from 4.9% to 5.5% and NNT ranging from 18 to 20. Results for all thresholds are presented in table 2 and figure 2.

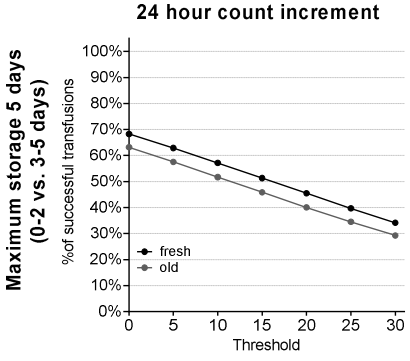

Figure 2: Percentage of successful transfusions as judged by the 24 hour absolute count increment, according to different thresholds for success

Table 1: Underlying distribution of fresh and old platelets and total number of studies and transfusions included in the analyses, according to different contrasts of old and fresh platelets.

Outcome Contrasts	Number of studies	Transfusions			Increment		
		Total	Fresh	Old	Mean fresh	Mean Old	Standard deviation*
24 hour absolute count increment							
Maximum storage 5 days (0-2 vs. 3-5 days)	5	3,063	581	2,482	16.15	11.47	33.97
1 hour corrected count increment							
Maximum storage 5 days (0-2 vs. 3-5 days)	15	18,049	4,113	13,936	14.32	12.21	8.03
Extreme difference (0-2 vs. 5-7 days)	10	6,693	3,341	3,352	13.93	11.24	6.54
24 hour corrected count increment							
Maximum storage 5 days (0-2 vs. 3-5 days)	15	6,813	2,165	4,648	8.26	6.91	8.76
Extreme difference (0-2 vs. 5-7 days)	8	2,393	1,003	1,390	8.78	7.43	7.29

*Combined for fresh and old

Corrected count increment

For the 'Maximum storage 5 days' contrast (0-2 versus 3-5 days), for corrected count increments thresholds ranging from 0 to 15, based on the 1 hour corrected count increment, the percentages of failed transfusions ranged from 4% to 54% for fresh platelets and from 6% to 64% for old platelets. This corresponded to differences, between old and fresh transfusions, ranging from 2.7% to 10% and NNT ranging from 37 to 10. After 24 hours these differences ranged from 4.3% to 6.2% and NNT ranged from 16 to 23. Results for all thresholds and for the 'Extreme difference' storage time contrast (0-2 versus 5-7 days) are presented in table 2 and figure 3.

DISCUSSION

As expected, we observed substantial differences in the percentage of failed and successful transfusions between fresh and old platelets. These results further indicate that between one out of 16 and one out of 37 transfusions with 3-5 day-old platelets will be considered failed while transfusions with 0-2 day-old platelets could have been successful. This two-and-a-half-fold difference is mostly due to the inclusion of results for the 1 hour corrected count increment, where the percentage of successful transfusions is influenced strongly be the chosen threshold. When considering 24 hour absolute or corrected count increments, numbers needed to treat were more stable between 16 and 23 (average 20), even for thresholds ranging from 0 to 30 for absolute count increments and from 0 to 15 for corrected count increments.

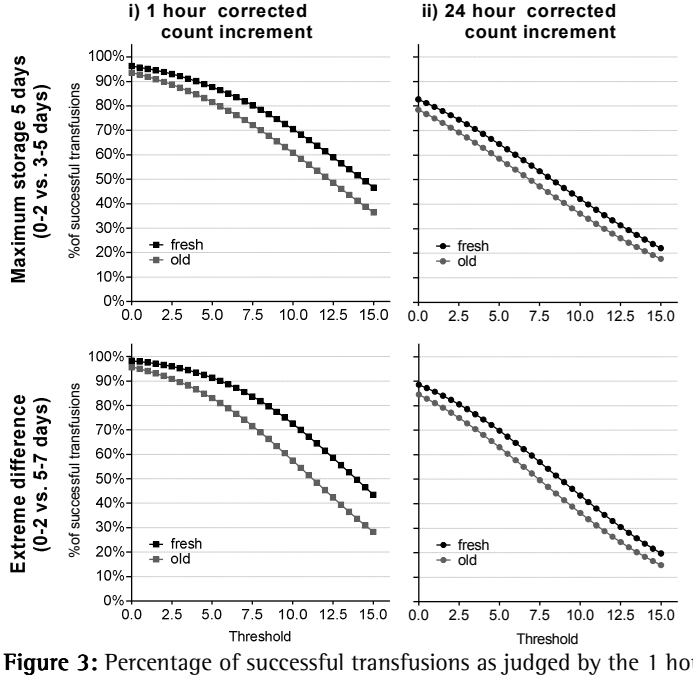

Figure 3: Percentage of successful transfusions as judged by the 1 hour and 24 hour correct count increment, according to different thresholds for success and different definitions of fresh and old platelets

Table 2: Percentage of failed transfusions judged by absolute and corrected count increments, according to different contrasts of fresh versus old platelets and different thresholds for success.

Absolute count increment				Corrected count increment			
Threshold	Fresh (% failed)	Old (% failed)	Difference (%)	Threshold	Fresh (% failed)	Old (% failed)	Difference (%)
1 hour increment, contrast: Maximum storage 5 days (0-2 vs. 3-5 days)							
0	NA	NA	NA	**0**	3.72	6.41	2.69
5	NA	NA	NA	**2.5**	7.04	11.32	4.27
10	NA	NA	NA	**5**	12.28	18.45	6.17
15	NA	NA	NA	**7.5**	19.77	27.86	8.09
20	NA	NA	NA	**10**	29.52	39.15	9.63
25	NA	NA	NA	**12.5**	41.03	51.44	10.41
30	NA	NA	NA	**15**	53.38	63.59	10.21
24 hour increment, contrast: Maximum storage 5 days (0-2 vs. 3-5 days)							
0	31.72	36.79	5.07	**0**	17.27	21.52	4.25
5	37.13	42.45	5.32	**2.5**	25.52	30.74	5.22
10	42.81	48.28	5.47	**5**	35.47	41.39	5.92
15	48.65	54.14	5.50	**7.5**	46.53	52.71	6.18
20	54.51	59.92	5.41	**10**	57.87	63.82	5.95
25	60.27	65.48	5.21	**12.5**	68.58	73.86	5.28
30	65.82	70.73	4.91	**15**	77.92	82.24	4.32
1 hour increment, contrast: Extreme difference (0-2 vs. 5-7 days)							
0	NA	NA	NA	**0**	1.66	4.28	2.62
5	NA	NA	NA	**2.5**	4.03	9.07	5.03
10	NA	NA	NA	**5**	8.62	16.99	8.37
15	NA	NA	NA	**7.5**	16.29	28.35	12.06
20	NA	NA	NA	**10**	27.41	42.46	15.05
25	NA	NA	NA	**12.5**	41.36	57.61	16.25
30	NA	NA	NA	**15**	56.51	71.70	15.20
24 hour increment, contrast: Extreme difference (0-2 vs. 5-7 days)							
0	NA	NA	NA	**0**	11.43	15.42	4.00
5	NA	NA	NA	**2.5**	19.45	24.96	5.51
10	NA	NA	NA	**5**	30.20	36.96	6.76
15	NA	NA	NA	**7.5**	43.02	50.39	7.38
20	NA	NA	NA	**10**	56.62	63.78	7.16
25	NA	NA	NA	**12.5**	69.48	75.66	6.18
30	NA	NA	NA	**15**	80.30	85.04	4.74

NA: not available, meta-analyses was not performed because less than 5 studies reported the outcome.

The true success of a platelet transfusion, should of course be measured by its haemostatic effect. It has been suggested that the relevance of storage time is very limited in this context.[13,14] This makes it even more worrisome that clinically relevant decisions, such as the decision to start diagnostic work-up for suspected platelet transfusion refractoriness, are still based on platelet count measurements, which do depend on storage time. If a blood bank supplies predominantly older platelets it would be likely to supply two consecutive old transfusions and a blood bank supplying predominantly fresh platelets would be likely to supply two consecutive fresh transfusions. Recipients from the 'old-supplier' are then likely to be deemed refractory one out of 16 to 23 times, where they would not have been considered refractory, if they had received transfusions from the 'fresh supplier'.

Being aware of this potential problem does not necessarily solve it. Clinicians might well be aware that two consecutively failed transfusions with older platelets do not necessarily indicate refractoriness to platelet transfusions. However, the mere fact that the two failed transfusions were with older platelets does not rule out refractoriness either. Therefore, out of precaution, every two consecutively failed transfusions should still be treated with similar

caution, even if the transfused platelets were 'old'. As a result, customers of a blood bank with predominantly older platelets are likely to start additional, unnecessary diagnostic work-up and raise unnecessary concerns in about one out of every twenty patients.

Similarly, seasonal differences in average storage time, or storage time differences related to blood groups could result in unnecessary concerns, since they are more likely to result in the transfusion of two consecutive old units. However, as mentioned above, knowing two units were old does not excuse a clinician from considering refractoriness for that patient. After all, the majority of transfusion failures occurring after transfusion of old units are completely storage time independent and therefore indicative of real refractoriness of the patient. After a single failed transfusion a clinician might still consider ordering a fresh unit for the next transfusion, if local blood supply logistics allow. However, if a patient is really refractory, any delay in diagnostic work-up will also result in a delay of appropriate treatment. Therefore, this option would be less preferable after multiple failed transfusions.

One solution for this problem could be to calculate increments corrected for storage time. However, for this measure to be useful in clinical practice would also require good consensus about which threshold should then be used to judge a transfusion as successful or failed.

Currently, there is not even consensus about the threshold for absolute and conventional corrected count increments. Reaching a consensus for the threshold for the "storage time-corrected count increment" would first mean reaching international consensus about the calculation of this measure. We therefore call experts in the field to suggest relevant calculations, simple enough to be applicable to daily clinical practice. In the meantime, the relatively large variation observed in estimates derived from 1 hour counts, might suggest the use of 24 hour increments, either absolute or corrected, to be preferable.

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Appendix – percentage of successful transfusions: formulas

Given: i: the studies indicator

j: the fresh/old indicator

$\bar{x}_{ij}$: the mean in the j^{th} category (fresh/old) of the i^{th} study

SD_{ij}: the standard deviation in the j^{th} category (fresh/old) of the i^{th} study

n_{ij}: the sample size in the j^{th} category (fresh/old) of the i^{th} study

$SE_{ij} = SD_{ij} \times \sqrt{n_{ij}}$ by definition the standard error (SE) is the standard deviation (SD) times the square root of the sample size (n)

τ^2: the inter-study variation from the DerSimonian and Laird random effect model

From the individual studies we estimated the meta-analyses pooled mean ($\bar{x}_j$) and the standard deviation (SD_j) for the fresh and old platelets separately based on the random effects model, following the steps:

1. The estimate of the combined effect for heterogeneity is defined as the inverse of the variance: $w_j = \left(1/\sum({SE_{ij}}^2 + \tau^2)\right)$ (i.e. the weight of each study under the random effects model)
2. $SE_j = 1/\sum w_j$ by definition the SE is the inverse of the sum of the studies weights
3. $\bar{x}_j = (\sum \bar{x}_{ij} \times w_{ij})/\sum w_{ij}$ (i.e. the pooled effect size of each group)
4. $n_j = (\sum n_{ij} \times w_{ij})/\sum w_{ij}$ (i.e. the pooled sample size of each group)
5. $SD_j = SE_j \times \sqrt{n_j}$ (by definition)

The probability of success is given by: $P(X \geq threshold)$ where $X \sim N(\bar{x}_j, SD_j)$ and the pooled (fresh/old) standard deviation is: $SD = \Sigma(n_j - 1)s_j^2/\Sigma(n_j - 1)^{1/2}$

Reference

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