Platelet Refractoriness

a report by
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The Problem

It has been shown that about 7,000 platelets per microlitre are consumed each day to repair the microvasculature.[1] In healthy subjects, whose physiological platelet counts mostly range from 150,000 to 400,000 platelets per microlitre, the consumption of 14,000 platelets per microlitre would have no clinical impact. Conversely, during profound thrombocytopenia even small increases in the average daily consumption of 7,000 platelets per microlitre can deprive the patient of a minimum platelet reserve and translate into catastrophic bleeding episodes. The traditional platelet transfusion policy adopted in the 1980s of ensuring that the patient's platelet count remained above 20,000 platelets per microlitre[2] was consistent with the above consideration. More recently, this level was reduced to 10,000 platelets per microlitre in stable onco-haematology recipients based on several prospective studies showing non-significantly different bleeding risks at the two platelet transfusion thresholds,[3] although a very recent study challenges the validity of this reduction.[4]

In spite of the consolidated effectiveness of platelet support in most recipients, clinical haematologists treating onco–haematological patients frequently experience the difficulty of managing platelet transfusion recipients who show – occasionally or repeatedly – inadequate post-transfusion increments of the platelet count. Such patients, who are called 'refractory' to platelet support when inadequate increments are detected on at least two sequential transfusions, represent a challenge as they are exposed to the risk of developing severe haemorrhage when the platelet count decreases below values usually considered 'safe'.

What Increments of the Platelet Count Should We Expect After an Average Platelet Transfusion Is Given to an Average Adult Patient?

Recent experimental evidence from the Trial to Reduce Alloimmunisation to Platelets (TRAP) study[5,6] supports the view that, in the average adult leukaemia patient receiving a platelet product containing about 400 billion platelets, an increment measured one hour after the end of the transfusion can be considered 'adequate' if it exceeds 10,000 platelets per microlitre. In that study – where the average patient showed a body surface area of 1.91m^2 and the average platelet transfusion contained 408 billion platelets – the mean one-hour increment was 24,900 platelets per microlitre. In addition, the study showed that the average post-transfusion platelet count increment decreased to 12,000 – approximately half – on the next day and that the time to next transfusion averaged 1.75 days.

Why do we conclude that a one-hour post-transfusion increment as 'low' as 10,000 platelets per microlitre can be considered 'adequate' given that the average increment is about 2.5 times greater? The answer to this question requires a simple preliminary arithmetic exercise, such as that reported in *Table 1*. Note that theoretical post-transfusion increments are almost twice as high as those observed. Thus, what is the cause of the 50% reduction from the theoretical 48,355 to the realistic increment of 24,900 detected, and why do we consider 'adequate' a value that is so much lower than the theoretical one? First, extensive clinical experience shows that several factors – most notably body temperature greater than 38.5°C, bleeding, infection and splenomegaly – significantly reduce platelet increments. Second, during platelet support a proportion of recipients develop alloantibodies to platelet antigens, which can determine rapid platelet clearance from the circulation. Third, platelets develop a storage lesion during their shelf life of five days and 'old' platelets determine lower increments than 'fresh' ones.

These considerations triggered the development of a simple method to compare the effectiveness of different platelet doses transfused into patients of different sizes. In this method, the increment is adjusted according to the patient's body surface area (BSA, a parameter correlated to blood volume) and the result is divided by the platelet dose. Based on a large set of experimental data, it was proposed and is currently accepted that 'corrected count increments' (CCIs) below 5,000 platelets per microlitre, detected 10–60 minutes after transfusion on more than one sequential occasions characterise patients who do not benefit from platelet support from random donors and are consequently called 'refractory'.[4,7,8] In the TRAP study, a CCI of 5,000 corresponded to an absolute average increment of 11,000 platelets per microlitre.[6] The above considerations and data support the previous statement that we can consider 'adequate' or 'acceptable' increments greater than 10,000 platelets per microlitre in the average patient transfused with about 400 billion platelets.

What Is the Frequency of Platelet Refractoriness?

In the large series of 528 acute leukaemia patients of the TRAP study, 143 (27%) became refractory.[6] In a previous cohort of 26 consecutive recipients of 266 platelet transfusions, 116 (44%) failed to produce a

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Table 1: Computation of a Theoretical Estimate of the Expected Platelet Count Increment One Hour After The Transfusion of a Given Number of Platelets Into a 75kg Male Patient

Variable 1	Platelet transfusion dose, e.g. 408 x 10^9
Variable 2	Patient's blood volume (0.075 x kg bodyweight in males), e.g. 0.075 x 75kg = 5.625l
Correction factor	Spleen 'early' sequestration of about one-third of transfused platelets
Computation	408 x 10^9 platelets: 5.625l x 2/3 = 48,355 platelets per microlitre

satisfactory increment, non-immune factors being considered responsible for the ineffectiveness in 88% of cases.[9] Another investigation performed in 252 onco-haematology recipients detected the presence of platelet-reactive antibodies (mostly against human leukocyte antigens [HLAs]) in the serum of 113 patients (44.8%).[10] The frequency of alloimmunisation is even higher in patients suffering from severe aplastic anaemia, as indicated by a study on 150 patients, 62% of whom developed platelet alloimmunisation.[11] As expected, the type of blood component represents an important factor related to the frequency of platelet alloimmunisation and alloimmune refractoriness.

Supporting the evidence from the TRAP study,[5] an investigation from Canada showed that the routine adoption of filtration leukoreduction was associated with a significant reduction in both platelet alloimmunisation and alloimmune platelet refractoriness. Values decreased from 19 to 7% and from 14 to 4%, respectively.[12]

What Can We Do to Support Refractory Patients?

The resolution of non-immune causes of refractoriness belongs to the general domain of global supportive therapy.[2,3,13–17] It can be difficult to resolve a septic episode, correct coagulopathy secondary to disseminated intravascular coagulation, reduce the size of an enlarged spleen or avoid using some drugs that have a negative impact on platelet survival.[18] In these cases, the natural course of the disease can prevail over the therapeutic tools available to the clinician. Conversely, a synergistic strategy between clinician and transfusion specialist can re-establish the efficacy of platelet support in refractory patients whose refractoriness depends on platelet alloimmunisation.

Two strategies can be adopted in these cases: the selection of HLA-compatible donors from large registries of HLA-typed blood and bone marrow donors[19,20] or the selection of compatible platelets by a cross-matching procedure. In our hospital the latter strategy is able to provide effective platelet support (post-transfusion increments greater than 10,000 per microlitre) in three-quarters of cases.[21] Several reports in the literature indicate that similar effectiveness can be obtained with the HLA-typing approach. The choice between the two strategies depends on local organisation. The main discriminatory factor is the availability of a large panel of HLA-typed blood donors.

Conclusions

In spite of significant strides towards its resolution, platelet refractoriness is still a transfusion complication that cannot be prevented or corrected in a relatively small, but not a negligible, proportion of recipients.[15] Therefore, it is necessary to perform additional studies to ensure the prevention of primary and secondary alloimmunisation to platelets and to improve the management and resolution of clinical factors capable of reducing the effectiveness of platelet support, not only for the clinical negative impact of refractoriness, but also for its high cost. In the study reported by Meehan et al.,[22] refractory and non-refractory patients had median hospital stays of 35 days compared with 14.4 days and inpatient hospital costs of US$103,956 compared with US$37,818, respectively. In our study,[20] in which 40 refractory patients received a mean of 14 cross-matched platelet transfusions over a period of 33 months, we determined that each refractory patient generated an average expense of €4,325 just for the solid-phase, disposable kit required for the selection of compatible platelets.[13] Labour costs should be added to this sum.

Finally, despite the importance of all of the numbers and numerical factors that have been discussed in this article (platelet dose, platelet count increments, CCIs, etc.), the fundamental element in ensuring the best possible outcome of platelet support is the close co-operation between a skilled transfusion medicine specialist and an experienced clinician able to identify clinical conditions associated with a high risk of bleeding, patients with significant co-morbidity and those with early signs of haemorrhage.[23] ■

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