# Scientific & Technical Report

STRPltQlty10.05

# Pool and Store Platelets – Augmenting Quality Platelet Supply to Meet Transfusion Requirements

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## Overview

In an effort to meet platelet transfusion requirements, platelets pooled prior to storage (referred to as pool and store [P&S] platelets) may prove to be an acceptable alternative when apheresis product is not available. In order to make an informed decision regarding the comparability of buffy coat (BC) or whole blood-derived (WB-d) P&S platelets with apheresis product, four questions need to be answered:

1. Can the quality of apheresis or single donor platelets (SDP) be considered comparable to WB-d or BC platelets that are pooled prior to storage?

2. Can platelet products be pooled to consistently provide platelet counts that are comparable to those found in an SDP product?

3. Is donor exposure, to mediators of morbidity inherent in any one donor, increased by pooling to the point where it causes significant concern?

4. Can quality bacteria detection be applied to ensure the safety of the platelet product?

### 1. SDP vs. Pooled Platelet: Quality

There are data comparing SDP with pooled platelets.[1,2] There are also data comparing pooled platelets after storage with those that are stored before pooling.[3,4,5,6] However, there are no studies directly comparing pooled and subsequently stored platelets with SDP products. Therefore, we need to rely upon the accepted principle that, “things equal to the same thing are equal to each other”.

Complicating matters further is the European experience of using BC platelets compared with North America’s use of platelets derived from platelet-rich plasma (PRP). Platelet transfusions in the US are largely derived from SDP[7] produced with an apheresis machine. In contrast, platelets may be produced from whole blood through PRP centrifugation[8,9] or BC processes.[10,11,12] In either of these cases, the final products derive from pooling platelets from multiple donors. The exposure to multiple donors has been a source of concern to some.

To make things more complicated, many studies prior to 1989 were performed with platelets that were not leukocyte reduced (LR)[†] as LR has not yet become routine, whereas later, more and more products were LR. To remove LR as a confounding variable, we need to demonstrate that LR does not affect platelet quality. The rationale to LR all component blood products is well appreciated[13] and LR of blood components, including platelets, has been adopted as a standard of practice in many countries in Europe as well as Canada.[14] Although the US is close to full implementation of LR, it is not yet universally performed. Most current apheresis devices are capable of providing a LR product ready for transfusion.[15] In contrast, platelets from BC[16,17] or PRP[18] are accomplished by filtration.

#### Whole Blood or Buffy Coat-derived and SDPs are Comparable

LR does not alter SDP quality.[1] Prior to routine use of apheresis machines to effect LR, Sweeney and co-workers showed that apheresis-derived platelets LR by filtration are not significantly different from their non-LR counterpart in terms of platelet recovery or survival.[1] Dumont, et al demonstrated that WB-d platelet recovery and survival were compared with SDP product

[†] The abbreviation, LR will be used to represent any variation of leukocyte reduction, including leukocyte reduced as can be determined from the context in which it is used.

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and shown to be indistinguishable.[19] Therefore there is no need to distinguish LR status in studies of pooled vs. SDPs. And available data supports the first part of the 'equal to each other' principle.

As is true of every field, studies can be found at variance with most.[20] However, in a study comparing SDP product with BC-derived platelets in hematological malignancy patients, there was a storage time-dependent effect on corrected count increments (CCIs) but no differences in the CCIs between the two products when corrected for storage time[21] — a finding consistent with the majority of studies looking at these comparisons separately and cited above.

**Whole Blood and Buffy Coat-derived Platelets are Comparable**

BC platelets are not available in the US and PRP-derived platelet filtration processes must be applied to individual units of blood or blood products. When considering the central question about comparability to SDP products, it is reasonable to first show comparability between BC- and PRP-derived platelets. Thereafter, comparisons can be made interchangeably; whether comparing BC- with SDP or PRP-derived platelets with SDP.

LR does not alter WB-d platelet quality. Early work by Sweeney et al.[2] showed no statistically significant difference in platelet recovery or survival when comparing WB-d platelets with or without LR by filtration. These data suggest LR is not a confounding influence on platelet quality.

Comparing WB-d with BC-d platelets, Keegan et al[22] demonstrated comparable recovery and survival using $Cr^{51}$ and $In^{111}$ isotopically labeled platelets. These observations were extended to the use of indices of platelet quality measured in vitro including platelet count, mean platelet volume, pH, $pO_2$, $pCO_2$, glucose and lactate levels, lactate dehydrogenase (LDH) activity, and hypotonic shock response (HSR).[23] In more recent studies, the quality of BC and PRP derived platelets appears comparable except for residual white cells but stored well after 5 or 7 days.[24] There may be more residual WBC membranes with BC processes after LR is applied,[25] but there is no definitive position on the adverse effects, if any, of white cell membranes. Therefore, platelets derived from WB or BC may be viewed as comparable regarding quality and need no further distinction.

In a comparison between SDP, BC and PRP-derived platelets, there were no significant differences in either 1-6 or 18-24 hour CCI when transfusion was provided to patients with hematological malignancy.[26] In another study, CCI measured within 1 and 20 hrs for BC-derived, contrasted with apheresis, platelets showed no significant difference when adjusted for storage time.[27]

**Pre-storage Pooling Does Not Alter Platelet Quality**

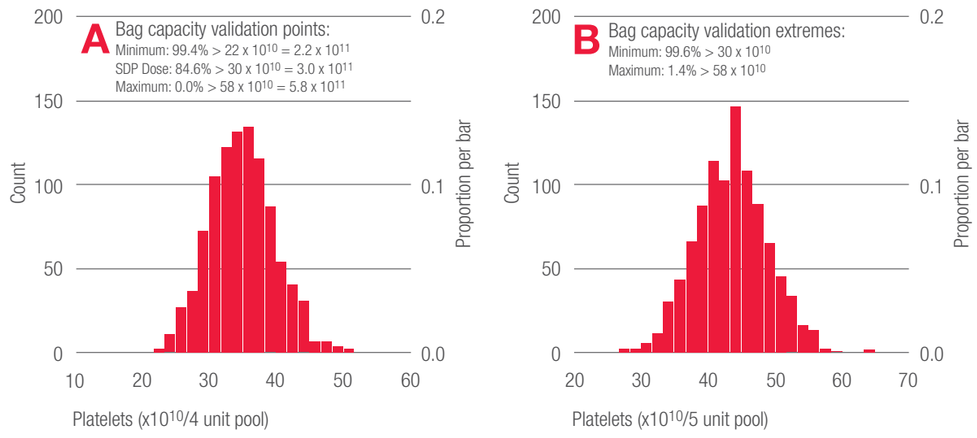
There is no differential effect of pooling for BC or WB-d platelets as relates to platelet quality. Pooled platelets were compared to those stored without pooling in an early study by Snyder and colleagues.[3] In addition to 1 and 24-hr CCIs, they showed there was no mixed lymphocyte reaction (MLR) as a consequence of pooling 4 units of platelets as determined by thymidine-$^3$H incorporation into cells. Moroff et al[4] extended these observations by using 6 and 8-unit pools with no change in MLR, pH, Kunicki morphology score, extent of shape change (ESC) induced by ADP, total ATP, aggregation response to ADP and collagen, HSR, LDH, and beta-thromboglobulin. More recently, P&S platelets were contrasted with conventional storage prior to pooling wherein it was shown no MLR occurs nor were any of the common indices altered in a clinically meaningful way.[28] And WB-d platelets showed no clinically important change in a variety of indices measured in vitro in a more recent study of pre-storage pooling.[5] Finally, WB-d platelets stored as a pool were contrasted with products pooled after storage with CCIs that were indistinguishable.[6]

Thus, there is evidence to show that WB-d platelets can be pooled prior to storage without altered effects on platelet quality both in vitro and in vivo, and SDPs are no different in quality than P&S platelets.

**2. P&S Platelets at a Consistent and Comparable Dose to SOPs**

In order to establish consistency and comparability of platelet dose of a pooled product relative to expected values for a SDP product, WB-d platelets were assayed for platelet count in 5 blood centers across the country. From one center to the next, the count varied slightly but overall the data suggest 4 to 5 unit pools will consistently provide platelet counts comparable to SDP requirements. The two panels in the figure show the frequency distribution of platelet counts with 4 and 5-unit pools (panel A & B, respectively).

SDPs must contain at least $3x10^{11}$ platelets in 90% of the samples tested.[29] Bags vary in capacity and these figures show that in the proposed containers to be used for pooling, 86.4% of the time the platelet content will be $3x10^{11}$ with 4 unit pools and 99.6% of the time with 5 unit pools. Moreover, capacity is never exceeded with the 4 unit pools and may be higher than desired in 1.4% of 5 unit pools. These data suggest that a product consistently meeting the requirements for platelet count set for SDPs can be achieved with a pooling of WB-d platelets.




**3. Donor Exposure**

The idea that exposure to multiple donors with pooled platelet products may increase the risk of serious infection with HIV or other mediators of morbidity prompted clinicians to consider SDPs as the preferred component blood product for platelet transfusion.[30] With the advent of nucleic acid testing for HIV, hepatitis C and other infectious agents, this argument is not strong as it once was. Consider the following examples (Dr. Joseph Sweeney – personal communication).

The risk of HBV infection is 1:200,000 with NAT. That represents 1 HBV for every 200,000 SDP units transfused. Further consider an institution providing 10 transfusions/patient x 100 pts/year that will total 1,000 transfusions/year. The time it takes to have a patient contract an infection is calculated to be 200,000 units/1,000 transfusions/year that equates to 200 years/HBV transmission. For an institution providing 5 unit pools the time is divided by 5 and the rate of infectivity becomes 1 in every 40 years. In this way, the risk may be considered real, but small. This assumes that all platelet recipients live past the incubation period of 6 months.

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Moreover, the argument of donor exposure issues may be flawed by the following logic. Unpublished data (courtesy of Dr. Joseph D. Sweeney – personal communication) show that markers of platelet storage, notably phospatidylserine expression on the surface of platelets, indicate that 20-30% of platelets store poorly and undergo apoptosis. This is confirmed by a concomitant decrease in the expression of Gp1b.

If true, then patients receiving a full dose of such components may be at greater risk for receiving an inadequate product than a recipient receiving a pooled platelet product where the presumed inferior quality product may be diluted by the remaining units in the pool. Moreover, there are reasons to believe that platelets derived from a single donor might bring with them a larger dose of mediators of morbidity (such as lipids or anti-leukocyte antibodies thought to be mediators of transfusion related acute lung injury).

### 4. Bacteria Detection

Recently, the AABB[31,32] and College of American Pathologists (CAP)[33] mandated that all platelet products be tested for contamination with bacteria. It is possible to argue that in many instances, tests applied to WB-d platelets are different from those used with SDPs since they often miss slow growing organisms.[34,35] The WB-d platelets are tested largely at hospital blood banks who use pH or glucose meters or indicator strips as opposed to well-characterized FDA market cleared devices.[36,37,38] Thus there is evidence to support the view that FDA market cleared devices perform better than other methods and that differential application leads to blood products with disparate standards. Since the same method of bacteria detection used for SDP is envisioned to apply to P&S platelets,[39] this makes these two component blood products more comparable in terms of quality and cost.

## Summary

SDPs have long held a preferred position among transfusion experts.[40] However, the evidence presented suggests a new perspective, with P&S platelet products reasonably viewed as a complementary strategy to meet platelet transfusion needs.

In vitro and in vivo data reviewed here suggest that SDP and P&S platelets, ABO-matched and pooled in a manner consistent with cGMP are comparable in quality, and using 4 to 5 unit pools, P&S platelets can be prepared to consistently provide comparable platelet counts.

Since the advent of NAT, the concern over donor exposure to viruses is not as clinically meaningful as it once was. Bacteria testing has further increased the safety of platelet transfusions.

It is well known that apheresis donors are sometimes more difficult to recruit as evidenced by the fact that not all blood centers can satisfy their platelet requirements with single donor products. P&S platelets will provide a product to meet the needs of platelet transfusion requirements that cannot be satisfied with SDP products alone.

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