Plateletapheresis: indicators of product quality

This white paper provides an overview of the key in vitro and in vivo quality matrixes for plateletapheresis products and discusses the reported differences of these indicators between different technologies .

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Apheresis is the process of collecting blood components such as plasma, platelets, red blood cells, and leukocytes from donor blood. Whole blood from the donor is separated by the device through centrifugation and/or filtration, based on the cell sedimentation speed and/or affinity to filtration media. The selected component of the anticoagulated blood is retained, while remaining blood components are returned to the donor through automated circulation. Cell separators employ either continuous flow centrifugation, which uses 1 or 2 venipunctures to collect blood, or intermittent flow centrifugation, or filtration which returns the unselected blood components to the donor after it is temporarily collected in the cell separator. In practice, apheresis presents several considerations. For example, apheresis requires a trained operator; is difficult in emergency settings; requires moderate capital expenditures; and although may result in adverse reactions among donors, such as paresthesia, tingling, seizure, and muscle cramps, has a high safety-to-risk ratio. These adverse reactions mostly result from the use of citrate anticoagulants during apheresis.

The collection and use of blood components through apheresis has increased dramatically over the past few decades. The transfusion of blood components collected through apheresis has many benefits. Indeed, it provides larger quantities of components (representing a larger therapeutic dose) than does blood components derived from manual whole blood collection, produces a more consistent product content, makes efficient use of the donor, reduces the donor's blood cell count recovery times, and decreases the risk of bacterial contamination of the final transfusable products. By eliminating the recipient's exposure to multiple donors, apheresis additionally reduces the risks of human leukocyte antigen (HLA) alloimmunization and transfusion-transmitted diseases.[1-5]

Platelets are enucleate blood cells (150-450×10^3/µl) that form a platelet plug by adhesion and aggregation, thereby contributing to hemostasis.[6] Platelets are usually transfused for [7, 8]:

- treating hemorrhage due to severe thrombocytopenia
- prophylactically increasing platelet counts
- treating platelet dysfunction disease

Quality of the product

Platelet products that are stored at room temperature (20-24°C) with agitation may remain viable for 5 days or extended to 7 days if in conjunction with appropriate detection or reduction of bacterial contamination and depending on the type of additive solution and plastic containers.[9]

The quality of platelet concentrates (PCs) that are stored after donation is influenced by many factors including the preparation method of the PCs, the plastic material of the storage bag, the storage media (Different types of platelet additive solutions (PAS) or plasma), the storage conditions including duration of storage, the storage temperature, type of anticoagulant used, the concentration of PCs in the bag and the agitation.[10, 11] Platelet quality can be evaluated in vitro using several parameters such as visual appearance (swirling, absence of visible aggregates or platelet product color indicating possible contaminations with red cells), metabolic activity, volume, platelet count, pH changes

and white blood cell count (WBC) per unit. After transfusion, platelet recirculation can be evaluated using corrected count increment (CCI) and percentage platelet recovery (PPR) at 1 hour and 20 hours post transfusion which accesses the functional platelets in circulation. In non-hemorrhagic transfusion of platelets, if the CCI at 1 hr and 20 hours is < 7500 platelets/μL/m2 and < 4500 platelet/μL/m2 and PR at 1 hour and 20 hours <30% and 20% respectively on two consecutive occasions it indicates platelet transfusion refractoriness.[12, 13] Also, aggregation or viscoelastic in vitro testing can be used to assess the in vivo functionality of PC transfusions.[14]

White blood cell count

When recipient's white blood cells (WBCs) are exposed to transfused WBCs, allogenic immune reactions may result in complications. In such cases, the leukoreduction process is employed to reduce the complications that were induced by the transfusion. The decision to leukoreduce is motivated by several major goals: reducing febrile non-hemolytic transfusion reactions, diminishing HLA sensitization and platelet refractoriness, reducing the rate of cytomegalovirus infection, and reducing the rate of transfusion-associated graft versus host disease.[15,16] Latest generation apheresis instruments feature in-process leukoreduction techniques, or integrated leukoreduction filters that eliminate the need for further, post-apheresis reduction of leukocytes counts. Leukoreduced blood products are required to meet AABB guidelines, which indicate that WBC counts per unit must be $<5\times10^6$. In Europe, the EDQM recommends that the WBC per unit needs to be $<1\times10^6$ with >90% of controlled units required to be within the threshold.[9] Additionally, in some countries as for example in France, the local authority ANSM recommends stricter thresholds of $<1\times10^6$ with >97% of controlled unites required to be within the threshold, leading to the need to add an additional leukocyte filtration step on some devices featuring in-process leukoreduction.[17] The residual WBC content in a platelet product has been significantly associated with the total product yield collected, with higher products yields presenting higher residual levels of WBC.[18] Published residual WBC can be found in table 1.

	Amicus Double-needle	Cobe Spectra V7-LRS Double-needle	Amicus Single-needle	Trima Accel Single-needle	Com.TEC V4 Single-needle	MCS+ UPP Single-needle
WBC ($\times10^6$) (average)	0.3 [19] 90 [20] 0.05 [21]	0.09 [20]	1.56 [22]	0.18 [18] 0.16 [23] 0.4 [21]	0.57 [19] 1.17 [22]	0.04 [23]
% of yield with WBCs $<1\times10^6$	94 [19] 100 [24] 95.6 [21]	95 [24]	96 [25] 16 [22]	98.7-99.7 [18] 96.7 [23] 100 [21]	87 [19] 50 [22]	99.2 [23]
% of yield with WBCs $<5\times10^6$	100 [19] 100 [24] 98.9 [21]	95 [24]	100 [25]	100 [18] 100 [23] 100 [21]	100 [19]	100 [23]

Table 1. Residual white blood cell count (WBC) per dose

Red blood cell count

Red cell contamination of platelet product occurs during plateletapheresis and results from ineffective separation of red cells and platelets. Currently, there are no general quantified standards of acceptability of red cell contamination for plateletpheresis units. However, the AABB standards recommend compatibility testing when an apheresis platelet contains more than 2 ml of red cells (ref AABB standard 24th ed 5.14.5). Furthermore, the Transfusion Act of the German Medical Association in agreement with the Paul Ehrlich Institute sets the level of residual RBCs at $<3x10^9$/unit. Additionally, pathogen inactivation technologies require stricter standards as for example with Intercept at $<1x10^9$/unit ($<4x10^6$/ml and assuming a 250 mL unit). Recently, platelets products collected on the Trima Accel system have been reported from routine quality controls to contain almost 3 times more residual RBC than platelets collected on the MCS+ device (4.36×10^8/unit vs. 1.5×10^8/unit; $p<0.001$) but with both technologies delivering products within the current guidelines.[23]

Visual Appearance

The visual appearance of platelets, such as evidence of swirling, is used to simply evaluate platelet morphology.[26] Swirling is caused by light interferences when a discoid platelet is exposed to a light source. Generally, platelet concentrates with a pH of 6.7-7.5 will show swirling when the platelets retain their discoid shape in vitro at the time of transfusion, and are expected to be functional in vivo.[26, 27] In the recent years limited data has been published about swirling in platelet apheresis products and specifically data that allows for comparison between multiple platforms. Tynngård and colleagues have compared COBE Spectra and Trima with no differences between swirling rates, with all products presenting maximum swirling.[11] A more recent study comparing the Amicus with COM.TEC platelet products resulted in the Amicus group a swirling score of 3 in 92% of the units and score of 2 in 8% of the units while the COM.TEC group presented 88% and 12% respectively.[22]

Platelet (PLT) aggregate formation in apheresis-derived PLT products has been known to occur, and their prevention was a point of high interest when component technologies were first developed.[28] Products with macroaggregates or clumps may be discarded due to concerns linked to efficacy and safety of the product. Discard may occur at different occasions, for example, at the blood center when detecting irreversible clumps, in the hospital blood bank when clumps remained undetected in the blood center or just formed when platelets were stored in the hospital blood bank, or on the hospital ward when clumps were not detected by the blood bank staff or formed during transport to the ward.[29, 30] Currently there is no consensus on a general discard strategy and procedures therefore vary from center to center. Some centers may discard all products with any residual aggregates at 24 h, and other centers might further process clumped units by eliminating those clumps by (leuco) filtration and discarding the ones still containing aggregates after the filtration process. Others release products only with less than a

specified number of microaggregates but no products containing macroaggregates. However, at the time of transfusion platelet product with no swirl or visible aggregate or abnormal color (i.e. red) is generally discarded.

By way of comparison, PLT aggregation in apheresis-derived PLT products – sometimes referred to as 'postpump clumping' or 'friendly clumping' – may also be related to the exposure of PLTs to centrifugal forces and shear stress (pumps) during collection which may lead to increased activation and possibly aggregation.[2, 21] PLT aggregates may dissipate during rest periods and agitation.[31] However, in some rare cases, the aggregates do not dissipate within 24 h postcollection and can persist longer even throughout the storage period.[21] Although aggregates occur regularly in PLT products, their relevance in terms of their impact on product quality, clinical efficacy and safety has never been systematically studied and publications referring to this aspect of PLT quality are scarce and often contain very limited information. Besides donor specific characteristics, also the utilized technic including the apheresis system contributes to an increased rate of units with platelet aggregates.[29, 32, 33] A recent survey to several blood banks has reported that Amicus or Trima apheresis systems are associated with higher levels of platelet aggregates.[33]

Metabolic activity

Metabolic activities of apheresis platelets are mainly measured using pH, pCO2, pO2, bicarbonate, glucose, lactate, adenosine triphosphate (ATP), and hypotonic shock response (HSR).

The AABB requires that the pH of the platelet products remains ≥6.2 during storage with agitation at 20-24°C while EDQM recommends a pH>6.4 during storage. During storage, pH decreases as a result of increased lactic acid production due to glycolysis. At pH 6.0, the platelets irreversibly transition from the discoid to the spherical form.[34] Accordingly, pH has been identified as an indicator of stored platelet function. However, Tudisco et al. found that pH had little utility for the quality control of platelets produced by MCS + LN 9000, Amicus, and CS-3000+ apheresis instruments.[35] Most platelet products obtained from apheresis collections have a pH ≥6.2 on day 5 of storage, and the pH may even exceed 7.0 at 7 days of storage.[36-41] However, in some studies statistical significances on pH levels were found between platelet products from different apheresis devices but still with pH ≥6.4 up to day 7 as reported by Macher and colleagues comparing Amicus with Trima platelet products.[42]

Assessments of pCO2, pO2, and bicarbonate changes in apheresis platelets showed that pCO2 and bicarbonate levels were both significantly reduced in all platelet concentrates collected using MCS+ LN9000 or Trima instruments. However, platelet product pO2 levels were observed to increase or decrease, depending on the sample. Furthermore, in apheresis platelets, glucose levels decrease and lactate significantly increases during storage.[36-40] Macher and colleagues found that in PCs from Amicus device comparing to PCs collected on TRIMA had lower glucose, and higher lactate as well as extracellular LDH, which reflects cytoplasmic leakage values, suggesting a higher PLT metabolism up to 7 days.[42] Additionally, Tynngård and colleagues reported that at day 5, TRIMA PCs had significant higher lactate concentration than COBE Spectra PCs.[41] Furthermore, the LDH values increased during the 7 days storage in PCs collected with the COBE Spectra whereas no significant changes were reported for the TRIMA PCs but no significant differences between the two devices were reported.[41]

ATP is the major energy source for platelet survival. Naturally, ATP also decreases significantly during storage.[36] For example, it has been reported that ATP was reduced by 42% in platelet concentrates collected using Trima from day 0 to day 7.[36, 37, 39]

HSR measures the capacity of platelets that have been restored to normal morphology after hypotonic shock due to the addition of a hypotonic solution. HSR is regarded as a predictor of platelet functionality.[37, 43] The HSR of apheresis platelets is very stable with small decreases as storage times increases.[37-41] The HSR results of PCs have been reported to be higher for TRIMA PCs comparing to Amicus PC at day 0 of storage but no significant differences after that.[42] No differences in HSR between COBE Spectra and TRIMA were found by Tynngård and colleagues but Spectra PCs had a significant lower HSR at day 7 comparing to day 5.[41]

Platelet activation

Platelets play two key roles in hemostasis: platelet adhesion to exposed subendothelial membrane and platelet aggregation among activated platelets result in platelet plug formation. Various studies have investigated platelet activation, which has been used to evaluate platelet quality during processing and storage of plateletpheresies products. Activated platelet markers that have been used in studies of plateletpheresis include P-selectin (CD62P)[12, 19, 44], CD63 [37, 45, 46], glycoprotein (GP)Ibα [44, 47, 48], CD40 ligand (CD40L, CD154)[49-53], and coated platelets.[54, 55] Furthermore, also in vitro platelet aggregation tests have been explored to access the functionality of plateletpheresies products.[32, 41, 42, 56]

P-selectin (CD62P) is stored in granules of endothelial cells and platelets. It is expressed on the surface of activated cells, where it functions as a cell adhesion molecule.[19, 44] During storage, increased P-selectin expression on activated platelet surfaces triggers rapid clearance of transfused platelets from circulation. Comparisons of platelet concentrates obtained from different apheresis instruments have demonstrated that the double-needle Amicus has higher rates of P-selectin-positive platelets than does the single-needle Trima Accel: this suggests that increased P-selectin expression may result from prolonged processing times within the centrifuge of the apheresis device.[12, 42, 44] However, no differences were observed between the P-selection expression in the platelet products of COBE Spectra and TRIMA nor between Amicus and COM.TEC.[22, 41]

CD63 is a 53-kDa lysosomal membrane glycoprotein that is translocated to the platelet membrane after platelet activation. It is considered to be a platelet activation marker.[57] Gutensohn

et al.[45] reported that the CD63 levels of platelets collected using Amicus, Cobe Spectra, and Trima devices increased after storage for 5-8 days.[37, 46]

CD40L, a member of the tumor necrosis factor family, is a trimeric transmembrane protein that is mainly contained within platelets.[49, 52] CD40L is generally sequestered inside resting platelets. However, it translocates to the cell surface after activation, and is subsequently cleaved from the platelet surface to generate soluble CD40L (sCD40L). Therefore, increased sCD40L levels can provide a marker of platelet activation.[49-53] Platelet products that are collected with MCS+, Trima Accel, and Amicus instruments show increased sCD40L levels during storage.[51-53] Further, the sCD40L levels of platelet products that are collected using the Amicus or Gambro instruments do not differ substantially the sCD40L levels of platelet products that are prepared from whole blood.

Coated platelets provide another marker of platelet activation. Coated platelets are activated by collagen and thrombin, representing approximately 30% of the total platelet population.[54, 58] The surfaces of coated platelets contain procoagulants.[54, 58] The percentage of coated platelets that is obtained from whole blood and apheresis products decreases as post-production storage time increase. The plateletpheresis method has also been observed to influence platelet activation; in addition to the storage phase itself, the plateletpheresis process conducted with the Trima System decreases the number of coated platelets.[54, 55]

Finally, the in vitro platelet function can be measured by platelet aggregometry or viscoelastic testing. Apelseth and colleagues reported that the TEG kaolin test MA values can be correlated with fewer bleeding episodes in leukemia patients treated with plateletapheresis units.[14] Additionally, it has been reported that the % of aggregation reduces significantly with storage.[36] Macher and colleagues found the platelet products from Amicus to be more activated than Trima products and at the same time to be significantly less responsive to aggregation stimuli.[42] Furthermore, Jilma-Stohlawetz and colleagues confirm the pervious results and reported the MCS+ platelet products to be significantly more functionally responsive to aggregation stimuli than Trima or Amicus platelet products.[56]

Corrected count increment (CCI) and percent platelet recovery (PPR)

When evaluating the in vivo recovery and survival of post-transfusion platelets, CCI and PPR are routinely used to determine the response to platelet transfusions in vivo, as well as to assess platelet transfusion refractoriness. Successful platelet transfusion is defined as a CCI greater than 7,500 platelets × m2/µl and a PPR greater than 30% within 1 hour of transfusion.[59] In a quality evaluation of apheresis platelet products, Pandey et al.[59] found that use of the COM.TEC instrument provided an optimal response to platelet transfusion, in terms of both CCI and PPR values. However, Julmy et al.[12] reported that the transfusion efficacy of the double-needle Amicus was significantly lower than that of the single-needle Trima Accel. Julmy et al. [12] considered this finding to be a consequence of high platelet concentrations or increased platelet activation, showing that Amicus is not suitable for high-yield plateletpheresis (≥6.0×10[11]). On the other hand, Slichter and colleagues have reported that MCS+ platelet products are associated with higher platelet recovery.[40] The published CCI of different plateletapheresis technologies can be found in table 2.

	Amicus Double-needle	Cobe Spectra Double-needle	Trima Accel Single-needle	Com.TEC Single-needle
CCI 1hour × 10^3/µl	7.9 [12]	19.8 [60]	15.6 [12] 28 [61]	10.1 [59]

Table 2. Corrected count increment (CCI)

Conclusion:

Various studies have evaluated the quality of platelet products during apheresis platelet storage and several platelet quality markers have been developed specially looking at platelet activation. The processing method and additive solutions used have been reported to impact these quality markers in addition to donor specific characteristics. However, there is currently limited data comparing the quality of platelet products generated by different types of plateletpheresies devices. Most of current studies comparing different plateletpheresies devices look into the product yield and device performance but overlook the quality of the final products generated. Furthermore, significant differences in quality markers have been reported between platelet products coming from different plateletpheresies devices. Even though, most of these differences are within the main platelet product quality standards, there are significant differences between standards of different countries. Future studies are required to assess if the observed differences between the platelet quality of different plateletpheresies devices have a clinical impact in patient outcomes.

About the Author

Dr. Mark Popovsky was Clinical Associate Professor of Pathology at Harvard Medical School and Beth Israel Deaconess Medical Center for more than 20 years. He has served on 7 editorial boards, authored more than 375 peer-reviewed publications, published 2 reference books on transfusion medicine, and served on many national and international committees. He served as Chief Medical Officer of Haemonetics for 15 years and is currently serving as a medical consultant to the company.

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