SAFETY AND EFFICACY OF SEVEN DAY PLATELETS

Concerns over bacterial proliferation in room temperature–stored platelet concentrates prompted the US Food and Drug Administration on June 02 1986 to issue a memorandum to blood establishments directing a reduction in the allowable storage time of platelet concentrates from 7 to 5 days.[1] In this memorandum, the FDA called attention to several cases of fatal post-transfusion sepsis from platelet transfusions that had been reported to the agency and stated that "significant levels" of bacteria may be seen in platelets after 5-7 days of storage. At that time, no FDA cleared bacterial detection devices were available for use with platelet concentrates. The platelet storage period had been increased from three days to 5 days in 1981 with the introduction of new plastics and further increased to 7 days in 1984 using the same container materials. The temporal whiplash in the permissible storage times for platelets that collection establishments and hospitals experienced in the 1980s abated as the 5-day permissible storage period was unchanged until recently, with the exception of one aborted clinical trial described below.

The prospect for a longer storage period was raised in 2002 when two culture-based bacterial detection systems were cleared by the FDA for testing platelets shortly after collection, eBDS (Pall, now Haemonetics) and BacT/ALERT® (bioMérieux). These devices have been adopted for use universally in the US, in part driven by the AABB (Standard 5.1.5.1 for Blood Banks and Transfusion Services introduced in 2004) and the College of American Pathologists (Transfusion Medicine Checklist item 44955 (culture requirement was first included in this item in 2004)). However, the sensitivity of these devices has been demonstrated to be only between 11 and 47%[2]

With the availability of the culture-based systems, in 2005, the FDA cleared leukoreduced platelets collected by apheresis with multiple devices for storage through 7 days at room temperature based on acceptable platelet performance. The efficacy of platelets stored for more than 5 days has been demonstrated in many studies (summarized below). However, in order to implement storage of apheresis platelets for up to 7 days, the FDA required a post-marketing surveillance study to assess the field performance of one bacterial screening method used as a release test. CaridianBCT, Inc. (formerly Gambro BCT, Inc., now TerumoBCT), initiated the study and was later joined by Fenwal, Inc. (formerly Baxter, Inc., now Fresenius Kabi). The primary objective of this post-marketing study (known as PASSPORT) was to demonstrate that 7-day licensed apheresis platelets when tested post-storage using the BacT/ALERT® device would not present a greater risk of a detectable bacterially contaminated unit than an untested platelet. In this study, bacterial culture was not performed at Day 5 but units were recultured on Day 8 ("Surveillance Test"). A total of 52 centers enrolled from September 2005 through April 2008 at which time the study was terminated owing to concerns by the study sponsors that the residual risk of a bacterially contaminated apheresis platelet labeled for 7-day storage was unacceptably high. Surveillance testing demonstrated four true positives of 6,039 tested (662/million; 95% CI, 180-1695/million). There was concern that the 662/million residual risk of a cultured platelet

was greater than the release test yield of 231/million, indicating poor culture test sensitivity. In fact, the authors, while noting the study as completed was underpowered, stated that the data suggested that the bacterial contamination rate was approximately 1/1000. With the total surveillance population of only 6,039, the study did not demonstrate with 95% confidence that the residual risk of the BacT/ALERT®-screened platelet was less than that of an unscreened platelet. They also concluded that "additional actions or testing may be required" to further reduce the residual septic transfusion risk of cultured apheresis platelets even with a 5-day storage limitation. As a result of the study's findings, 7-day storage of platelets was not deemed permissible at that time, despite demonstrated efficacy.[3]

Let's turn to the efficacy of platelets stored for more than five days. While the published studies summarized below used different methodologies and devices, taken together they illustrate conclusively that platelets stored for 5 days are clinically efficacious. Readers are referred to the publications for details that are beyond the scope of this report.

Dumont et al. collected 24 apheresis platelets and on Days 5 and 7 of storage alternately labeled them with ^{51}Cr and ^{111}In to determine recovery and survival. Component pH was maintained in the range 6.2 to 7.61 through 7 days and did not detrimentally affect either in vitro or in vivo outcomes. In vitro platelet characteristics were adequately maintained over 7 days. As would be expected, Day 5 platelets had better recovery (63.0 ± 4.36 vs. 53.9 ± 4.36%, $p < 0.0001$) and survival (161 ± 8.1 vs. 133 ± 8.1 hour, $p = 0.006$) than Day 7 platelets. The authors concluded that "although declines in recovery and survival were noted, these are less than used previously to gain licensure of 7-day storage and are unlikely to be clinically significant. Extension of storage to 7 days could be implemented with bacterial screening methods to select out contaminated components without a significant effect on the platelet efficacy compared to 5-day components."[4]

Dijkstra-Tiekstra et al. studied pooled buffy coat-derived leukoreduced platelets stored for 2 to 7 days after blood collection. These were administered to clinically stable thrombocytopenic patients. For 7-day-old platelets, 76 of 78 (97%) of the transfusions resulted in a count increment at 1 hour of at least 10,000/ul and 37 of 39 (95%) in a corrected count increment at 1 hour of at least 7,500, which were levels supportive of clinical success. Mean ± SE values of count increment at 1 hour and corrected count increment at 1 hour of 7-day-old concentrates were 28,700/ul±2,300 (n = 78) and 19,000±2,000 (n = 39), respectively. No significant differences were observed between 5- and 7-day-old concentrates transfused with respect to count increment at 1 hour and corrected count increment at 1 hour. The authors concluded the in vivo results showed that the platelets they studied can be stored for up to 7 days with excellent clinical results, provided that they are routinely screened for bacterial contamination.[5]

Vassallo et al. collected sixty apheresis products for in vitro and in vivo studies. Using dual radiolabels (^{111}In and ^{51}Cr), recovery and survival values for 6-day and 8-day stored platelets (N = 18) were compared. Mean Day 6 recovery was 53 ± 11%

compared with 49 ± 11% for Day 8. Survival values were 163 ± 31 and 154 ± 31 hours, respectively. Mean Day 1, 6, & 8 pHs(22°C) were 7.4 ± 0.1, 7.2 ± 0.2 and 7.0 ± 0.3, respectively. Only one evaluable unit had a pH value of less than 6.2 at Day 8. The authors concluded that the storage of apheresis platelets for 8 days appeared acceptable, as assessed by laboratory testing and in vivo radiolabeled studies.[6]

AuBuchon et al. evaluated the in vitro characteristics and in vivo viability of leukoreduced platelet units derived from platelet-rich plasma stored for 5 days versus 7 days. Two whole-blood units collected two days apart were studied from each donor in a paired design. These were leukoreduced (Leukotrap PL) and stored for 7 and 5 days. Post-storage samples from test and control units were randomly labeled with ^{51}Cr or ^{111}In and simultaneously infused autologously to determine recovery and survival. Small but significant ($p<0.05$, paired t test) differences between 5 and 7 days of storage were seen in in vitro variables such as extent of shape change, hypotonic shock response, morphology, and P-selectin expression. In vivo recovery declined on average 11 percent with the two additional days of storage from 54.4±13.6 to 48.7±15.0 percent ($p<0.002$); survival decreased on average from 6.7±1.0 to 5.4±1.7 days ($p<0.002$). Storage for 7 days was associated with reduced recovery and survival and in vitro variables, suggesting extension of the storage lesion. These differences, however, were small in magnitude, and the authors concluded that they were "unlikely to have significant clinical effects."[7]

Shanwell et al. studied apheresis platelets from ten donors stored in an additive solution. They divided the collections into 2 equal units for a paired comparison. Platelets in one unit were ^{111}In-labeled at 1 day of storage, and platelets in the other unit were ^{111}In-labeled after 7 days of storage. Platelet recovery on Day 7 was 80 percent of the recovery on Day 1 ($p < 0.05$), and the survival on Day 7 was 65 percent of survival on Day 1 ($p < 0.005$). The authors concluded that the recovery and survival results, as well as in vitro parameters studied, were acceptable clinically according to a proposed standard by Murphy which has come to be accepted by the FDA.[8,9]

Slichter et al. studied in vitro platelet function and metabolic assays on apheresis platelets both on Day 0 and after 8 days of storage. They also performed in vivo platelet recovery and survival studies on fresh donor samples compared to Day 8 stored platelets. The fresh and stored autologous platelets were labeled with either ^{51}Cr or ^{111}In, and the radiolabeled platelets were transfused. Recoveries averaged 66 ± 16 percent versus 53 ± 20 percent and survivals averaged 8.5 ± 1.6 days versus 5.6 ± 1.6 days, respectively, for fresh compared to 8-day-stored platelets. After 8 days of storage, the in vivo post-transfusion recovery and survival of autologous apheresis platelets met the proposed standards for post-storage platelet quality.[9,10]

Subsequently, Slichter et al. studied platelet recovery and survival using ^{111}In or ^{51}Cr in 58 normal subjects. They found that platelet recoveries decreased by 2.6% and survivals by 0.3 days/storage day. They concluded the data suggested "if stored platelet bacterial contamination issues are resolved, significant extension of platelet storage time (up to 8 days) would be possible."[11]

The studies summarized above address in vitro function and radiolabeled platelet recovery and survival and demonstrate that Day 7 platelets are comparable to Day 5 platelets with small or modest reductions in recovery and survival. Ultimately, the more significant indication of their efficacy are *in vivo* data, and the next 2 studies speak to the clinical effectiveness of platelets as they age in storage.

Maclennan et al. recently published a noninferiority, crossover trial in which they compared platelets stored for 6 to 7 days to platelets stored for 2 to 5 days. Greater than 80% of the platelets transfused were from apheresis collections, the remainder were pools of buffy coat-derived platelets. Stable hematology patients were allocated to receive blocks of 2 to 5 day or 6 to 7 day platelets in random order. The primary outcome was the proportion of successful transfusions during the first block, defined as a corrected count increment of more than 4,500 at 8 to 24 hours post-transfusion. Of 122 patients with an evaluable first block, 87 (71%) and 84 (69%) had successful transfusions after 2 to 5 day and 6 to 7 day platelets of mean (SD) ages of 3.8 (1.0) and 6.4 (0.5) days, respectively. Six to 7 day platelets were noninferior to 2 to 5 day platelets since the upper confidence interval (CI) limit was less than the predefined noninferiority margin of 10% (95% CI, -14.0% to 9.1%; p=0.766). Mean (SD) 8 to 24 hour corrected count increments were 9,400 (7,900) and 7,700 (7,100) after transfusion with 2 to 5 day or 6 to 7 day platelets (95% CI -3,310 to 30; p=0.054). The proportions of days with bleeding scores of Grade 2 or higher were 13% (38/297 days) and 11% (32/296 days; 95% CI, -3.2 to 7.2; p=0.454). Median interval to next platelet transfusion (2 days) was unaffected (95% CI, -10.5 to 5.4; p=0.531). The authors concluded that in stable hematology patients, there was no evidence that 6 to 7 day platelets were inferior to 2 to 5 day platelets, as measured by the proportion of patients with successful transfusions, bleeding events, or the interval to next transfusion. The finding of clinical non-inferiority supported the change to the routine provision of 7 day platelets in the United Kingdom which has significantly improved management of platelet inventory. The authors stated that the availability of extended shelf-life platelets is likely to have contributed to the reduction found in platelet wastage since this change was implemented.[12]

With respect to platelets stored for 5 days, Triulzi et al. reviewed the records of 650 hematology and oncology patients receiving either apheresis or pooled whole blood-derived platelets for whom the first transfused unit was stored 0 to 2 days for 48 patients (7%), 3 days for 158 patients (24%), 4 days for 223 patients (34%), and 5 days for 221 patients (34%). Overall, 131 of the 650 patients (20%) experienced ≥ grade 2 bleeding. Platelet storage duration did not predict time to first ≥ grade 2 bleeding (P = .87).[13]

The studies presented above used a variety of collection systems, platelet components, and test methodologies. Collectively, the reports conclusively demonstrate the efficacy of platelets stored for 7 days. The FDA has now presented a permissible pathway utilizing the Platelet PGD® test from Verax Biomedical for the immediate implementation of 7-day stored apheresis platelets in plasma in the US that takes into account their safety as well as their efficacy.[2] The FDA containers previously cleared for 7 day

platelet storage had been limited to 5 days solely due to the lack of an acceptable method for determining bacterial status close to the time of platelet transfusion. Due to this 5 day limitation, the most recent National Blood Collection and Utilization Survey documents an aphereis platelet outdate rate of 12.8 percent annually in the US.[14] The storage of platelets for more than 5 days provides for reduced outdating as well as improved availability and inventory management. The straightforward pathway institutions can take now to implement 7-day shelf-life for platelets will be addressed in detail in another White Paper.

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