Impact of the Duration of Platelet Storage in Critically Ill Trauma Patients

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Background: There is increasing evidence that the duration of red blood cell (RBC) storage negatively impacts outcomes. Data regarding prolonged storage of other blood components, however, are lacking. The aim of this study was to evaluate how the duration of platelet storage affects trauma patient outcomes.

Methods: Trauma patients admitted to a Level I trauma center requiring platelet transfusion (2006–2009) were retrospectively identified. Apheresis platelets (aPLT) containing $\geq 3 \times 10^{11}$ platelets/unit were used exclusively. Patients were analyzed in three groups: those who received only aPLT stored for $\leq$3 days, 4 days, and 5 days. The outcomes included mortality and complications (sepsis, acute respiratory distress syndrome, renal, and liver failure).

Results: Three hundred eighty-one patients were available for analysis (128 received aPLT $\leq$3 days old; 109 = 4 days old; and 144 = 5 days old). There were no significant demographic differences between groups. Patients receiving aPLT aged = 4 days had significantly higher Injury Severity Score ($p = 0.022$) and were more likely to have a head Abbreviated Injury Scale $\geq$3 ($p = 0.014$). There were no differences in volumes transfused or age of RBC, plasma, cryoprecipitate, or factor VIIa. After adjusting for confounders, exposure to older aPLT did not impact mortality; however, with increasing age, complications were significantly higher. The rate of sepsis, in particular, was significantly increased (5.5% for aPLT $\leq$3 days vs. 9.2% for aPLT = 4 days vs. 16.7% for aPLT = 5 days, adjusted $p = 0.033$). For acute respiratory distress syndrome and renal and liver failure, similar trends were observed.

Conclusions: In critically ill trauma patients, there was a stepwise increase in complications, in particular sepsis, with exposure to progressively older platelets. Further evaluation of the underlying mechanism and methods for minimizing exposure to older platelets is warranted.

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The ability to bank blood products is one of the most important advances in the history of transfusion medicine. For trauma care providers, this has allowed for a near on-demand availability of the full range of potentially lifesaving blood components. With our increasing understanding of the importance of early resuscitation with blood and its component parts, this is critical for providing the best available evidence-based care to the injured patient. By buffering the logistics of supply and demand, the ability to store blood products facilitates transportation and redistribution, minimizes wastage, and allows for the accumulation of reserves to be used in times of disaster. The ability to store blood products, however, is finite. Each component has a set lifespan and within these limits, each component undergoes degradation as it nears its expiration date.

Following the principles of inventory management, blood products are dispensed starting with the oldest available unit. Understanding the impact of the age of these products on patient outcomes is therefore important.

For unaltered red blood cells (RBCs), the maximum lifespan under ideal storage conditions is 42 days. Within this time frame, however, as the product nears its expiration date, changes occur to the constituent cells. These units, the oldest available, will thus be the first units to be dispensed. As a result of this, as demonstrated in the CRIT study,[1] a prospective, multicenter observational study of 284 intensive care units (ICUs) in the United States, the average age of the blood dispensed was 21.2 days. In a study sampling of 1,136 patients from 145 Western European ICUs,[2] the average age of blood transfused was 16.2 days. For RBCs, this transfusion of older units has been demonstrated to impact outcomes.[3–6] In the largest study to date of RBC transfusions during cardiac surgery, the impact of blood stored for $\leq$14 days was compared with blood stored for >14 days.[7] Although leukoreduction was not standardized in the study design, older blood was found to be associated with a significantly increased risk of postoperative complications including renal failure and sepsis as well as both short- and long-term mortality. In a study by Spinella et al.,[8] trauma patients who received five or more units

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of blood were analyzed. Using a maximum age of <28 days compared with ≥28 days, the older blood was associated with an increase in deep vein thrombosis and death from multisystem organ failure. In the study by the Denver group, older blood was also associated with an increase in infection after major injury.[9] In the study by Weinberg et al.,[10] again, blood stored beyond 2 weeks was demonstrated to increase the odds of mortality, despite leukoreduction.

With platelets, however, very little is understood about the impact of the duration of storage on outcomes. In a single retrospective analysis of platelet transfusion in patients undergoing cardiac surgery, no association of storage age with survival or postoperative infections was found.[11] Platelets are fragile and storage requires rigorous maintenance of a tightly controlled environment. The current Food and Drug Administration (FDA) approved lifespan for the majority of platelets is limited to a maximum of 5 days. Because of these conditions, and locoregional supply restrictions, maintaining a fresh inventory of platelets is difficult, especially for those blood banks with a low rate of turnover.

The purpose of this study was to evaluate how the duration of platelet storage affects trauma patient outcomes. Our hypothesis was that increasing storage times would be associated with deterioration in outcomes.

MATERIALS AND METHODS

After institutional review board approval, a retrospective review of the institutional trauma registry and the Blood Bank Database at the Los Angeles County + University of Southern California Medical Center was performed. All trauma patients who received a blood transfusion between 2006 and 2009 were identified. Patient variables abstracted included age, gender, blood group, injury mechanism, admission vital signs, Glasgow Coma Scale (GCS), hemoglobin, international normalized ratio and platelet count on admission, Injury Severity Score (ISS), Abbreviated Injury Scale (AIS), ICU length of stay (LOS), hospital LOS, complications (acute respiratory distress syndrome [ARDS], sepsis, acute renal failure [ARF] and liver failure), and mortality.

The number of RBCs, plasma, platelets, cryoprecipitate, and factor VIIa units transfused was abstracted from the Blood Bank Database. In addition, for RBC, plasma, and platelets, the duration of storage of each unit transfused was extracted. For RBCs, a separate analysis was performed for those units with a 28-day lifespan (28-day RBC) and a 42-day lifespan (42-day RBC). For both plasma and platelets, in addition to the volume and age of units transfused, an ABO-mismatch analysis was performed to correct for any adverse impact of exposure to nonidentical, compatible, or incompatible plasma contained within the donor platelets. Each unit transfused was correlated in terms of ABO compatibility with the recipient blood type. For both plasma and platelets, ABO identical transfusion was defined as a group A recipient receiving group A donor plasma/platelets, group B receiving group B donor plasma/platelets, group O receiving group O plasma/platelets, and group AB receiving group AB plasma/platelets. Compatible but not ABO identical plasma/platelet transfusion was defined as group O recipients receiving group A, B, or AB plasma/platelets as well as group A and B recipients receiving group AB plasma/platelets. Noncompatible plasma transfusion did not occur in this patient cohort. A noncompatible platelet transfusion was defined as a group A recipient receiving group B or O donor platelets; group B recipient receiving group A or O donor platelets; and AB recipients receiving group A, B, or O donor platelets. During the study period, apheresis platelets (aPLT) containing $\geq 3 \times 10^{11}$ platelets per unit with a maximum lifespan of 5 days were used exclusively. Data were entered into a computerized spreadsheet (Microsoft Excel 2003, Microsoft, Redmond, WA) and analyzed using SPSS for Windows, version 12.0 (SPSS, Chicago, IL).

Continuous variables were dichotomized using the following clinically relevant cut-points: age (≥55 vs. <55 years), systolic blood pressure at admission (<90 vs. ≥90 mm Hg), GCS at admission (≤8 vs. >8), ISS (≥16 vs. <16), and AIS (≥3 vs. <3).

The patients were divided into three cohorts: patients who received exclusively aPLT that had been stored for ≤3 days, 4 days, and 5 days. Patients who received platelets of differing age groups were excluded. The primary outcome measure examined was mortality; the secondary outcome measures were complications, ICU LOS, and hospital LOS.

These three cohorts were analyzed for differences in demographics, clinical characteristics, and blood transfusion requirements using univariate analysis. Chi-squared or Fisher's exact tests were used to compare proportions, and analysis of variance was used to compare means.

Logistic regression modeling was performed to control for confounders that were significantly different at the $p < 0.05$ level between the aPLT groups. Adjusted odds ratio and 95% confidence intervals were calculated for each group. A Cox regression analysis was used to evaluate the association between the duration of aPLT storage and outcomes. In addition, to identify whether the duration of aPLT storage was independently associated with the outcomes examined, a Cox proportional hazard regression model was performed including all factors that had a $p < 0.2$ from the univariate analysis.

Values are reported as means ± standard deviation; median (range) for continuous variables and as percentage for categorical variables. All analyses were performed using the Statistical Package for Social Sciences (SPSS Mac), version 18.0.

RESULTS

During the 4-year study period, 2,315 (13.8%) of the 16,802 trauma patients admitted to the LAC + USC Medical Center received a blood transfusion. aPLT transfusion occurred in 665 (28.7%) of the transfused patients. After exclusion of the 284 (42.7%) patients who received aPLT of varying ages, 381 patients were available for analysis. Of those, 128 (33.6%) received aPLT ≤3 days old, 109 (28.6%) = 4 days old, and 144 (37.8%) = 5 days old (Fig. 1). Of patients receiving ≤3-day-old platelets, because of logistic reasons, the majority were 3 days old with only 14 (10.9%) patients receiving 2-day-old platelets and none receiving 1-day-old platelets. The number of units of aPLT

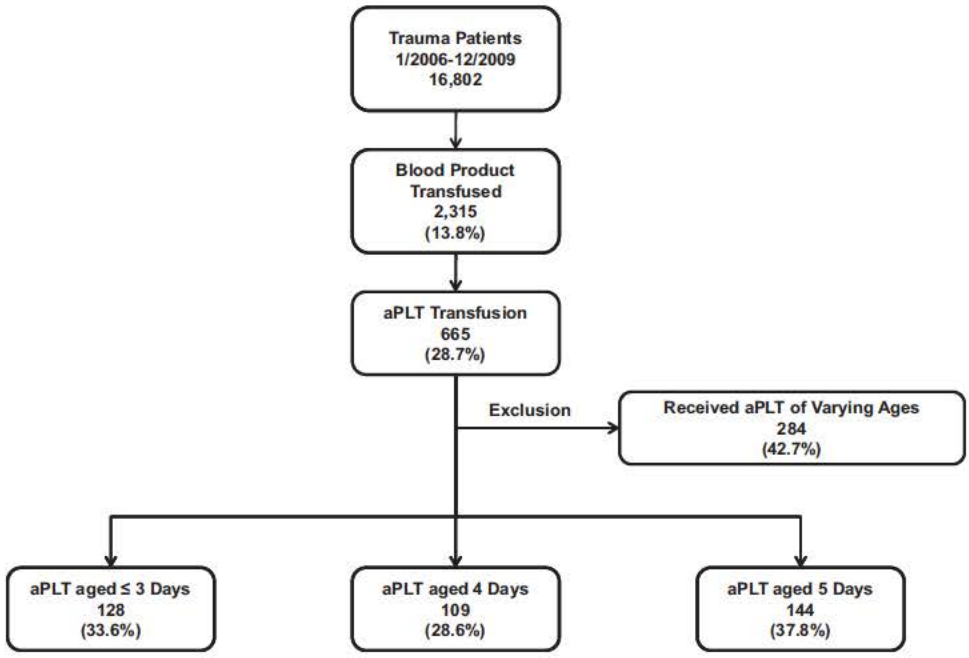

Figure 1. Study outline.

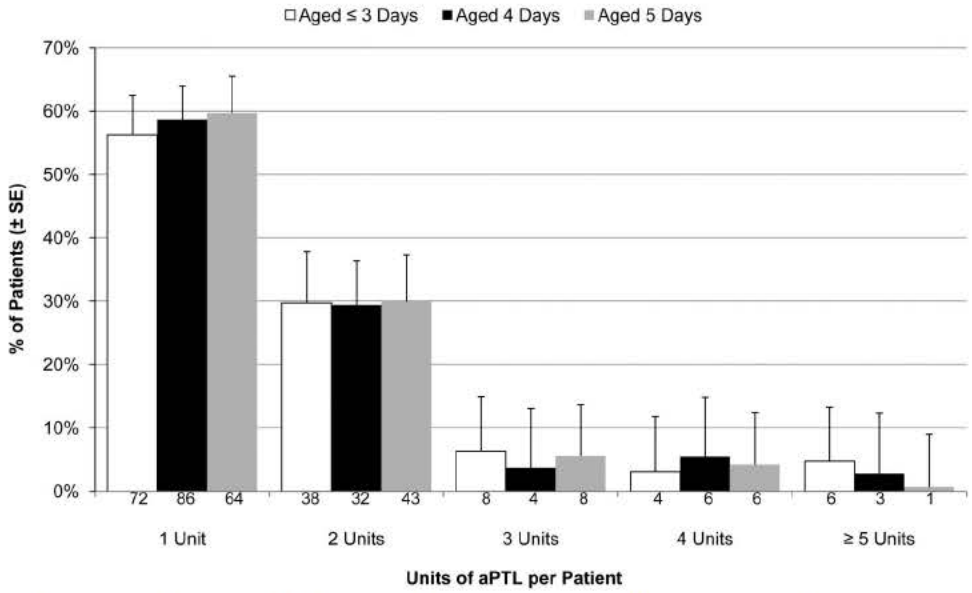

Figure 2. Number of units of apheresis of platelets transfused in relation to the percentage of patients receiving a platelet transfusion. The numbers beneath the columns represent the number of patients in each platelet age group. SE, standard error of the mean.

transfused per patient were similar among the three groups with the majority of patients receiving ≤2 units during their hospital stay (Fig. 2).

There were no significant differences in age (43.5 ± 21.6 for aPLT ≤3 days vs. 44.8 ± 24.4 for aPLT = 4 days vs. 42.3 ± 19.3 for aPLT = 5 days, $p = 0.634$) or gender (men: 83.6% for aPLT ≤3 days vs. 83.5% for aPLT = 4 days vs. 79.2% for aPLT = 5 days, $p = 0.560$) among the three groups. Patients receiving 4-day-old aPLT had a significantly higher ISS (21.5 ± 10.0 for aPLT ≤3 days vs. 25.5 ± 13.2 for aPLT = 4 days vs. 22.2 ± 12.4 for aPLT = 5 days, $p = 0.022$) and were more likely to have a head AIS ≥3 (43.8% for aPLT ≤3 days vs. 52.3% for aPLT = 4 days vs. 36.1% for aPLT = 5 days, $p = 0.014$). The demographic and clinical characteristics of the patient groups are summarized in Table 1.

Comparisons of transfusion requirements revealed no significant differences in volumes of aPLT, 28-day RBC or

TABLE 1. Demographic and Clinical Data of Patient Groups

	aPTL Aged ≤3 d (n = 128)	aPTL Aged 4 d (n = 109)	aPTL Aged 5 d (n = 144)	*p*
Age (yr) , mean ± SD; [median], (range)	43.5 ± 21.6; [40], (2–88)	44.8 ± 24.4; [40], (1–93)	42.3 ± 19.3; [40], (10–91)	0.634
Age ≥55 yr (%)	31.3% (40)	34.9% (38)	27.1% (39)	0.408
Male (%)	83.6% (107)	83.5% (91)	79.2% (114)	0.560
Blood group A	28.9% (37)	22.9% (25)	27.1% (39)	0.143
Blood group B	10.2% (13	11.9% (13)	6.9% (10)	
Blood group AB	6.3% (8)	1.8% (2)	2.8% (4)	
Blood group O	35.9% (46)	43.1% (47)	50.7% (73)	
Blunt (%)	66.4% (85)	71.6% (78)	66.7% (96)	0.637
Intubated on admission (%)	24.0% (30)	17.9% (19)	15.6% (22)	0.207
SBP on admission, mean ± SD; [median], (range)	117.3 ± 45.1; [125], (0–210)	118.4 ± 38.9; [120], (0–196)	123.9 ± 36.3; [123], (0–257)	0.362
SBP on admission < 90 mm Hg (%)	18.5% (23)	19.0% (20)	10.1% (14)	0.086
GCS on admission ≤8 (%)	28.7% (35)	33.0% (36)	30.9% (43)	0.775
HgB on admission, mean ± SD; [median], (range)	8.5 ± 2.3; [7.9], (3.7–15.5)	8.0 ± 2.3; [7.4], (3.4–13.9)	8.0 ± 1.8; [7.7], (3.8–13.9)	0.163
INR on admission, mean ± SD; [median], (range)	1.5 ± 1.4; [1.2], (1.0–12.9)	1.4 ± 0.7; [1.2], (0.9–5.5)	1.3 ± 0.5; [1.2], (0.9–4.3)	0.174
Platelet count on admission, mean ± SD; [median], (range)	219.5 ± 113.0; [218.0], (25–649)	217.1 ± 96.6; [213.5], (13–617)	236.4 ± 94.3; [235.0], (53–564)	0.339
ISS, mean ± SD; [median], (range)	21.5 ± 10.0; [22], (1–75)	25.5 ± 13.2; [25], (1–75)	22.2 ± 12.4; [20], (1–75)	0.022*
ISS ≥16 (%)	67.2% (86)	83.5% (91)	71.5% (103)	0.014*
Head AIS ≥3 (%)	43.8% (56)	52.3% (57)	36.1% (52)	0.036*
Chest AIS ≥3 (%)	39.8% (51)	40.4% (44)	42.4% (61)	0.905
Abdomen AIS ≥3 (%)	35.9% (46)	35.8% (39)	33.3% (48)	0.881
Extremity AIS ≥3 (%)	25.8% (33)	26.6% (29)	27.8% (40)	0.932

SD, standard deviation; SBP, systolic blood pressure; HgB, hemoglobin; INR, international normalized ratio.

* *p* values are significantly different ($p < 0.05$).

The *p* values for categorical variables were derived from χ^2 or Fisher's exact tests; *p* values for continuous variables were derived from analysis of variance. HgB values reported as gm/dl; platelet count reported as $\times 10^9$/L.

42-day RBC, plasma, cryoprecipitate, or factor VIIa among the three groups. In addition, the duration of storage of 28-day RBC, 42-day RBC, and plasma also did not differ significantly among the groups (Table 2). With 42-day RBC, for example, aPLT ≤3 days, aPLT = 4 days, and aPLT = 5 days groups received 11.6 units ± 8.7 units, 10.5 units ± 7.5 units, 10.7 units ± 9.5 units, respectively, $p = 0.837$. The mean age of the 42-day RBC received by each group was 26.7 days ± 5.6 days for aPLT ≤3 days, 26.6 days ± 5.4 days for aPLT = 4 days, and 28.0 days ± 6.9 days for aPLT = 5 days, $p = 0.468$. No difference in the ABO compatibility was found for plasma. However, for platelets, a significant difference in the rate of ABO incompatibility was seen (ABO compatible but nonidentical: 5.3% for aPLT ≤3 days, 16.1% for aPLT = 4 days, and 21.4% for aPLT = 5 days, $p = 0.004$) (Table 2).

When outcomes were compared according to the age of platelet transfused, there was no difference with regards to mortality (29.7% for aPLT ≤3 days vs. 40.4% for aPLT = 4 days vs. 25.7% for aPLT = 5 days, adjusted $p = 0.945$). However, those patients receiving the oldest aPLT, aged 5 days, had a significantly higher rate of overall complications when compared with those who received aPLT aged ≤3 days or 4 days (13.3% for aPLT ≤3 days vs.19.3% for aPLT = 4 days vs. 29.2% for aPLT = 5 days, adjusted $p = 0.005$). In particular, those patients receiving the oldest aPLT had a significantly higher incidence of sepsis (5.5% for aPLT ≤3 days vs. 9.2% for aPLT = 4 days vs. 16.7% for aPLT = 5 days, adjusted $p = 0.033$). For ARDS, ARF, and liver failure, similar trends were observed. No significant differences in ICU LOS or hospital LOS among the groups were found (Table 3).

Cox regression time to event analysis revealed early separation of overall complication-free curves for aPLT ≤3 days relative to those who received aPLT = 4 days or aPLT = 5 days (log rank: $p < 0.001$) (Fig. 3). This was also observed for sepsis (log rank: $p < 0.001$) (Fig. 4).

Cox proportional hazard regression was used to determine the independent risk factors associated with the development of overall complications. After controlling for differences in ISS, head AIS, and platelet ABO mismatch between the groups, there was a stepwise increase in the risk for complications with the duration of storage of aPLT transfused. Patients who received aPLT = 4 days and aPLT = 5 days had a 1.2-fold and 2.4-fold higher risk of developing complications, respectively, when compared with those receiving aPLT ≤3 days exclusively. In

TABLE 2. Transfusion Requirements of Patient Groups

	aPTL Aged ≤3 d (n = 128)	aPTL Aged 4 d (n = 109)	aPTL Aged 5 d (n = 144)	*p*
aPLT				
Mean units received	1.6 ± 0.8; [1], (1–3)	1.5 ± 0.7; [1], (1–3)	1.5 ± 0.7; [1], (1–3)	0.702
aPLT ABO mismatch				
ABO compatible but nonidentical (%)	5.3% (6)	16.1% (14)	21.4% (14)	0.004*
ABO compatible but nonidentical, mean units received	0.1 ± 0.3; [0], (0–2)	0.3 ± 0.6; [0], (0–3)	0.3 ± 0.7; [0], (0–3)	0.016*
ABO noncompatible (%)	1.4% (2)	2.3% (3)	1.6% (3)	0.952
ABO noncompatible, mean units received	0.03 ± 0.3; [0], (0–3)	0.05 ± 0.3; [0], (0–2)	0.04 ± 0.3; [0], (0–2)	0.097
28 d RBC				
Mean units received	1.0 ± 0.0; [0], (0–1)	1.3 ± 0.6; [0], (0–2)	1.6 ± 0.6; [0], (0–2)	0.289
Mean age of units received (d)	25.3 ± 2.3; [24], (24–28)	26.3 ± 2.1; [27], (24–28)	24.0 ± 7.8; [27], (10–28)	0.841
42 d RBC				
Mean units received	11.6 ± 8.7; [9], (1–33)	10.5 ± 7.5; [8], (2–32)	10.7 ± 9.5; [8], (1–53)	0.837
Mean age of units received (d)	26.7 ± 5.6; [26], (17–42)	26.6 ± 5.4; [27], (16–38)	28.0 ± 6.9; [27], (15–41)	0.468
Plasma				
Mean units received	6.9 ± 6.5; [5], (0–32)	6.7 ± 6.6; [4], (0–35)	7.3 ± 10.8; [5], (0–72)	0.505
Mean age of units received (d)	1.6 ± 0.6; [2], (1–4)	1.7 ± 0.6; [2], (1–3)	1.8 ± 0.7; [2], (1–5)	0.385
Plasma ABO mismatch				
ABO compatible but nonidentical (%)	11.8% (9)	12.9% (9)	15.2% (17)	0.790
ABO compatible but nonidentical, mean units received	0.3 ± 0.9; [0], (0–5)	0.4 ± 1.2; [0], (0–8)	0.5 ± 1.5; [0], (0–8)	0.364
Cryoprecipitate				
Mean units received	1.1 ± 4.2; [0], (0–33)	1.7 ± 4.2; [0], (0–22)	1.2 ± 4.1; [0], (0–22)	0.545

* *p* values are significantly different ($p < 0.05$).

All values are described as mean ± SD; [median], (range) unless otherwise specified. No transfusion of ABO noncompatible plasma was observed in any of the study groups. The *p* values were derived from χ^2 or analysis of variance.

TABLE 3. Outcomes

	aPTL Aged ≤3 d (n = 128)	aPTL Aged 4 d (n = 109)	aPTL Aged 5 d (n = 144)	Adjusted *p*
Mortality (%)	29.7% (38)	40.4% (44)	25.7% (37)	0.945
Overall complication (%)	13.3% (17)	19.3% (21)	29.2% (42)	0.005*
Sepsis (%)	5.5% (7)	9.2% (10)	16.7% (24)	0.033*
ARDS (%)	4.7% (6)	5.5% (6)	9.0% (13)	0.307
ARF (%)	5.5% (7)	5.5% (6)	8.3% (12)	0.396
Liver failure (%)	2.3% (3)	3.7% (4)	6.9% (10)	0.238
	Mean ± SD; [Median], (Range)	**Mean ± SD; [Median], (Range)**	**Mean ± SD; [Median], (Range)**	
ICU days	12.2 ± 21.6; [6], (1–181)	8.9 ± 8.7; [6], (1–52)	10.6 ± 21.6; [6], (1–181)	0.149
Hospital days	18.4 ± 25.4; [9], (1–182)	11.6 ± 12.1; [7], (1–57)	17.8 ± 23.2; [12], (1–206)	0.136

* *p* values are significantly different ($p < 0.05$).

The *p* values were derived from multivariable analysis for ICU LOS and HLOS; and from bivariate analysis for mortality and complications. The *p* values were obtained after adjustment for ISS, head AIS, and platelet ABO mismatch.

addition to the duration of platelet storage, chest AIS ≥3, hemoglobin on admission, GCS ≤8, and volumes and duration of storage of RBC were found to be independently associated with the development of complications (Table 4).

The analysis was repeated for patients who received platelets within the first 24 hours of hospital admission. A total of 53 patients (31.4%) receiving aPLT ≤3 days old, 57 patients (33.7%) = 4 days old, and 59 (34.9%) = 5 days old were included. When the outcomes were analyzed, no significant difference in mortality was found (34.0% for aPLT ≤3 days vs. 43.9% for aPLT = 4 days vs. 23.7% for aPLT = 5 days, adjusted $p = 0.101$). Those patients receiving the oldest aPLT, aged 5 days, had a trend toward a higher rate of overall complications when compared with those who received aPLT aged ≤3 days or 4 days (13.2% for aPLT ≤3 days vs. 17.5% for aPLT = 4 days vs. 28.8% for aPLT = 5 days, adjusted $p = 0.098$). In particular, those patients receiving the oldest aPLT had a higher incidence of sepsis (5.7% for aPLT ≤3

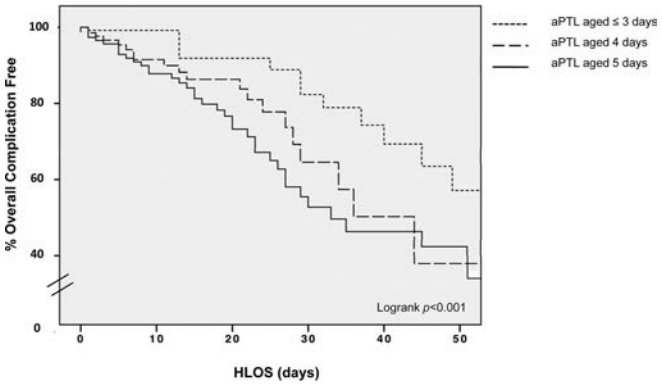

Figure 3. Cox regression time to event analysis for the development of overall complications by platelet age. HLOS, hospital length of stay.

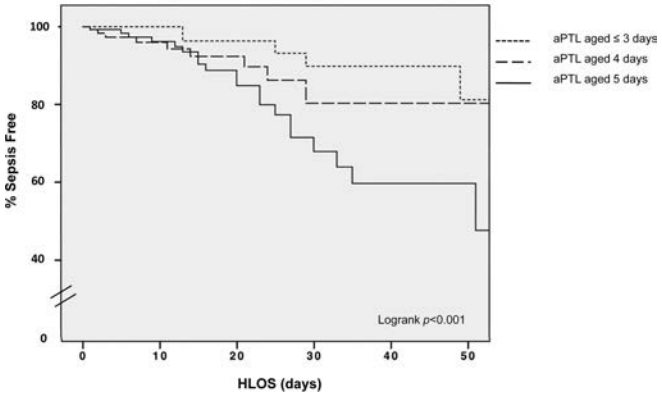

Figure 4. Cox regression time to event analysis for the development of sepsis by platelet age. HLOS, hospital length of stay.

days vs. 8.8% for aPLT = 4 days vs. 15.3% for aPLT = 5 days, adjusted $p = 0.223$). For ARDS, ARF, and liver failure, similar trends were observed.

DISCUSSION

Blood banking has undergone significant improvements over time and has now evolved to the point where in many areas of the world surgeons have ready access to a safe, stable supply of the full range of blood components. In the care of the injured patient, this has facilitated adherence to the best available evidence-based practices in resuscitation, operative, and postoperative care. This ability to accurately replace shed blood has become increasingly important as our understanding of the impact of blood component therapy on survival becomes clear.

For packed RBCs, several studies have examined the impact of storage time on outcomes. In a recent study from the Cleveland Clinic, for patients undergoing cardiac surgery, although leukoreduction was not standardized in this study, transfusion of RBCs stored for greater than 2 weeks was associated with an increase in complications and death.[7] In trauma patients specifically, Spinella et al.[8] demonstrated an increase in complications including thromboembolic complications and multisystem organ failure in patients who received five or more units of blood that had been stored for 28 days or longer. In the analysis by the Denver group, transfusion with old blood also resulted in an increased rate of infection.[9] Although the exact mechanism for this deleterious effect is not known, acute iron deposition and abnormal levels of plasma nontransferrin bound iron may be responsible for fueling a proinflammatory response.[6] This process may also be potentiated by noniron associated inflammatory agents within the stored blood. Simple mechanical changes because of prolonged storage have also been postulated to negatively impact function by impairing the deformability of the red cells.[12]

For platelets, however, very little is understood regarding the impact of prolonged storage times on outcomes. In a study from Duke,[11] coronary artery bypass grafting patients receiving a single unit of platelets with a known age were retrospectively examined. In this study, no effect on mortality or infection was seen.

For critically ill trauma patients, platelets are an important part of the resuscitation strategy. For patients requiring a massive transfusion, early work by Cinat et al.[13] demonstrated survivors received a higher platelet ratio than nonsurvivors. Data from Perkins et al.[14] evaluated 464 primarily penetrating combat casualties and reached a similar conclusion. A higher aPLT:RBC ratio was associated with improved survival at both 24 hours and 30 days. In a civilian series from Vanderbilt, patients receiving platelets at a ratio of 1:5 or greater had improved 30-day mortality,[15] and in the multicenter study by Holcomb et al.,[16] patients who received both a high ratio of plasma and platelets had improved 6- and 24-hour as well as 30-day survival. In the largest series to date specifically addressing platelet volumes, increasing platelet transfusion in ratios approaching 1:6 was associated with a stepwise improvement in survival at 12 and 24 hours as well as in overall survival to discharge.[17]

In this analysis, patients who received only platelets of a single known age were included. Care was taken to ensure that the study groups were homogeneous with respect to the volumes of platelets and where appropriate the volumes and age of RBCs, plasma, cryoprecipitate, and factor VIIa. Plasma and platelet ABO compatibility were also carefully controlled for as previous studies have shown that exposure to nonidentical plasma is associated with an increase in complications.[18,19] The exact mechanism responsible for this detrimental effect remains unknown. Differences between groups with respect to standard epidemiologic markers and injury demographics, admission clinical and laboratory values, as well as blood type were also accounted for. Although mortality was not affected, with increasing platelet age, the complication rate was significantly higher. In particular, the rate of sepsis was demonstrated to increase as the age of the platelets increased, with a trend toward the same for ARDS, renal, and liver failure. Blood product utilization in these injured patients occurs early during their hospital course and as would be expected because of this, the time to event analysis for overall complications and sepsis demonstrated early separation. The mechanisms responsible for this in-

TABLE 4. Cox Proportional Hazard Regression Model With Overall Complication as the Dependent Variable

Step	Variable	Overall Complications	r^2	Adjusted OR (95% CI)	Adjusted *p*
1	Chest AIS ≥ 3	28.8%	0.05	2.4 (1.4–4.1)	0.002*
2	HgB on admission	—	0.03	0.8 (0.7–0.9)	0.016*
3	GCS ≤ 8	28.1%	0.02	1.9 (1.1–3.4)	0.044*
	aPLT				
4	Aged ≤ 3 d	13.3%	0.08	—	—
5	Aged 4 d	19.3%		1.2 (0.6–2.7)	0.622
6	Aged 5 d	29.2%		2.4 (1.4–4.7)	0.021*
	42 d RBC				
7	Number of units received	—	0.04	1.1 (1.1–1.1)	<0.001*
8	Mean age of units received	—	0.03	1.1 (1.1–1.1)	<0.001*

OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; GCS, Glasgow Coma Scale score; HgB, hemoglobin; INR, international normalized ratio.

* *p* values are significantly different ($p < 0.05$).

Variables entered in the model: age, gender, blood group, injury mechanism, intubated on admission, SBP and GCS on admission, HgB, INR and platelet count on admission, ISS, AIS for each body region, units of RBC (lasting 28 and 42 d), plasma, aPLT, cryoprecipitate and factor VIIa received, duration of storage of units of RBC (lasting 28 and 42 d), plasma and aPLT received and platelet ABO mismatch. A total of 286 (75.1%) subjects with complete data were included in the model.

crease in complications are unknown. Platelets are fragile and banking of these metabolically active anuclear fragments requires adherence to strict storage conditions. In general, the maximum duration of storage at 20 to 24°C is 5 days. Longer period of storage, up to a maximum of 7 days, is possible if an FDA-approved storage system is used. During this time, platelets undergo morphologic and functional changes resulting in a decreased responsiveness toward physiologic agonists, a process often referred to as the "platelet storage lesion."[20–23] In addition, during storage, proinflammatory immunomodulators may also be released.[24] Direct microbiological contamination of the platelets may also occur. The optimal storage temperature for platelets is room temperature, an environment that is ideal for bacterial growth. Transfusion-related bacterial contamination remains a major ongoing cause of both morbidity and mortality.[25–28] In this analysis, although the infection could not be directly attributed to the transfusion of contaminated platelets or a negative immunomodulatory effect exerted by older platelets, infection was the most common complication seen, and a significant increase was demonstrated with each increase in the day of storage.

In this study, Cox proportional hazard regression was used to determine the independent risk factors associated with the development of complications. After controlling for differences in ISS, head AIS, and platelet ABO mismatch between the groups, there was a stepwise increase in the risk of complications with increasing duration of aPLT storage. In addition to the duration of platelet storage, however, chest AIS ≥3, hemoglobin on admission, GCS ≤8, and volumes and duration of storage of RBC were also found to be independently associated with the development of complications.

This study was limited by its retrospective design. There are errors inherent to any such study but in particular, those that use a trauma registry dataset for quantitative transfusion-related data. To mitigate these inaccuracies, transfusion data were extracted exclusively from the blood bank, where dispensing and utilization data are strictly regulated by the US FDA. These regulations mandate that blood banks maintain comprehensive records for each unit of platelet dispensed, and it is hoped that this decreased the errors associated with this retrospective study design.

This study was also limited by the fact that 42.7% of patients were excluded to allow for the analysis of groups that were homogeneous with respect to exposure to platelets of a specific age. The groups were very well balanced, however, with only minor differences in head AIS scoring and ISS. The remainder of the transfusion profile including the age, ABO compatibility and volumes of RBCs, plasma, cryoprecipitate, and factor VIIa were also tracked and balanced.

In addition, specific platelet function and culture data were not available for analysis. This may have permitted an understanding of the underlying mechanism behind the deterioration in outcomes that were seen. In fact, a direct temporal relationship between platelet exposure and outcomes could not be demonstrated because of the retrospective study design. Excluding those patients who received platelets after 24 hours to compensate for this temporal bias resulted in an insufficiently powered analysis; however, a similar trend toward increased complications was seen.

Finally, platelet age was analyzed in three distinct groups. Because of the logistics involved in platelet collection, processing, and distribution, as expected, no platelets at 1 day were available for analysis. For 2 days, only 10.9% were available. The remainder was well distributed across the remaining 3 days in sufficient numbers to allow a useful analysis. Although relatively rare, the impact of even fresher platelets warrants further investigation in the future.

Despite these limitations, these data demonstrated a progressive increase in complications, in particular sepsis with a trend toward the same for ARDS, renal, and liver failure as the platelets transfused neared their expiration date. The future role of "preservative" compounds or of cryopreservation to mitigate the effects of aging may help to improve the functional efficacy of our platelet supply and warrants further investigation.

CONCLUSIONS

In critically ill trauma patients, there was a stepwise increase in complications, in particular sepsis, with exposure to progressively older platelets. Further evaluation of the underlying mechanism and methods for minimizing exposure to older platelets is warranted.

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EDITORIAL COMMENT

Degradative changes inevitably occur during the conventional storage of blood components for transfusion, and collectively these changes have been labeled the storage lesion. The red blood cell has been the subject of the majority of investigation in this area, and a large number of both laboratory observations characterizing the red cell storage lesion and observational studies demonstrating associations between the transfusion of older red cells and adverse outcomes have been reported. Nonetheless, the clinical significance of the red cell storage lesion remains unclear, and a causal relationship between the transfusion of older blood and morbidity or mortality has yet to be substantiated.

The platelet storage lesion has also been described, including changes in platelet morphology and degranulation, and has been documented to commence after the first 24 hours of storage.[1] The limiting factor for platelet storage, however, is the risk for bacterial contamination that grows over time, hence the relatively short shelf life of 5 days for stored platelets. The clinical consequences of transfusing relatively old but not outdated platelets have, up to now, received little attention. In this issue of *The Journal of Trauma*, Inaba et al.[2] have taken an observational approach similar to what has been previously done with red cells to determine whether the transfusion of relatively older platelets is associated with morbidity and mortality in a cohort of trauma patients. They report a significant association between the transfusion of older platelets with sepsis and overall complications.

The authors could not, however, demonstrate a relevant temporal relationship between platelet exposure and outcome and acknowledge that an explanation for the observed association between the transfusion of older platelets and adverse outcomes is lacking. In fact, the selection bias known as confounding by indication inherent to these types of studies may account for the authors' findings.[3] In a trauma patient population, those who require platelet transfusion are by

nature more severely injured or ill than those who do not require platelets. And secondary to the supply limitations inherent to blood banking, patients who require platelet transfusions are more likely to receive relatively older platelets. The stage is then set for an incidental association between outcomes and platelet storage age. Statistical adjustment for severity of illness by Injury Severity Score or other parameters is unlikely to fully correct for confounding by indication and is an analytical limitation of not only this study but of all observational studies concerning transfusion and outcomes. Nonetheless, the observations reported by Inaba et al. are intriguing and certainly worthy of further investigation. Specifically, the platelet storage lesion must be further characterized so that mechanistic links between specific degradations that occur before storage outdate and adverse outcomes may be proposed.

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