The Impact of Platelet Transfusion in Massively Transfused Trauma Patients

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BACKGROUND: The impact of platelet transfusion in trauma patients undergoing a massive transfusion (MT) was evaluated.

STUDY DESIGN: The Institutional Trauma Registry and Blood Bank Database at a Level I trauma center was used to identify all patients requiring an MT (≥10 packed red blood cells [PRBC] within 24 hours of admission). Mortality was evaluated according to 4 apheresis platelet (aPLT):PRBC ratios: Low ratio (<1:18), medium ratio (≥1:18 and <1:12), high ratio (≥1:12 and <1:6), and highest ratio (≥1:6).

RESULTS: Of 32,289 trauma patients, a total of 657 (2.0%) required an MT. At 24 hours, 171 patients (26.0%) received a low ratio, 77 (11.7%) a medium ratio, 249 (37.9%) a high ratio, and 160 (24.4%) the highest ratio of aPLT:PRBC. After correcting for differences between groups, the mortality at 24 hours increased in a stepwise fashion with decreasing aPLT:PRBC ratio. Using the highest ratio group as a reference, the adjusted relative risk of death was 1.67 (adjusted $p = 0.054$) for the high ratio group, 2.28 (adjusted $p = 0.013$) for the medium ratio group, and 5.51 (adjusted $p < 0.001$) for the low ratio group. A similar stepwise increase in mortality with decreasing platelet ratio was observed at 12 hours after admission and for overall survival to discharge. After stepwise logistic regression, a high aPLT:PRBC ratio (adjusted $p < 0.001$) was independently associated with improved survival at 24 hours.

CONCLUSIONS: For injured patients requiring a massive transfusion, as the apheresis platelet-to-red cell ratio increased, a stepwise improvement in survival was seen. Prospective evaluation of the role of platelet transfusion in massively transfused patients is warranted. (J Am Coll Surg 2010;211: 573–579. © 2010 by the American College of Surgeons)

For the critically ill trauma patient who has sustained massive blood loss, the principles governing the acute resuscitation process have shifted, with an increased emphasis on aggressive blood component therapy.[1-5] This has been driven by both military[6-8] and civilian[9-17] data, supporting the use of plasma early, in ratios approaching 1:1 for patients requiring a massive transfusion (MT), defined in most research protocols as ≥10 units of packed red blood cells (PRBC) within the first 6 to 24 hours after admission.

The role of other blood components, such as platelets, however, is less clear. In theory, aggressive platelet transfusion is not unreasonable because it is a critical component of the functional clotting response to injury. Stored at room temperature and transfused as a type specific product, technically, the logistics of early aggressive platelet transfusion can be supported by most blood banking systems provided sufficient product is available. However, unlike the rapidly expanding evidence base exploring the impact that plasma exerts on mortality, relatively little is available to guide platelet transfusion in the resuscitation of critically ill trauma patients.[10,13 18-20]

The objective of this study was to determine the impact of an increasing platelet-to-PRBC ratio on the outcomes of

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Abbreviations and Acronyms

adj = adjusted
AIS = Abbreviated Injury Score
aPLT = apheresis platelet
GCS = Glasgow Coma Scale
ISS = Injury Severity Score
MT = massive transfusion
OR = odds ratio
PRBC = packed red blood cells

trauma patients who required a massive transfusion. Our hypothesis was that aggressive platelet transfusion improves survival.

METHODS

The Los Angeles County + University of Southern California Medical Center is an American College of Surgeons verified Level I trauma center. After approval by the Institutional Review Board, all trauma patients receiving a PRBC transfusion over a 9-year period ending in December 2008 were identified using the Institutional Trauma Registry and Blood Bank Database. A massive transfusion was defined as a transfusion of 10 or more PRBC units during the initial 24 hours after admission. Patient variables abstracted included age, gender, mechanism of injury (blunt vs penetrating), blood pressure on admission, Glasgow Coma Scale (GCS), Injury Severity Score (ISS), Abbreviated Injury Score (AIS) for each body region (head, chest, abdomen, extremity), and outcome. Continuous variables were converted into dichotomous variables using clinically relevant cut-points (age $\geq$ 55 years, systolic blood pressure $<$90 mmHg, GCS $\leq$ 8, ISS $\geq$ 25, AIS $\geq$ 3). The numbers of PRBCs, fresh frozen plasma (FFP), platelet, and cryoprecipitate units transfused at 12 hours, 24 hours, and at hospital discharge were abstracted from the blood bank database. During the study period, apheresis platelets (aPLT) containing $\geq 3 \times 10^{11}$ platelets per unit were used exclusively.

Patients were classified into 4 clinically relevant groups according to the aPLT:PRBC ratios received at 12 and 24 hours after admission: Low ratio ($<$1:18), medium ratio ($\geq$1:18 and $<$1:12), high ratio ($\geq$1:12 and $<$1:6), and highest ratio ($\geq$1:6). The primary outcomes measure tested was mortality at 12 and 24 hours as well as overall survival to discharge.

Statistical analysis

Differences in the demographic and clinical characteristics between the 4 platelet ratio groups were evaluated using analysis of variance.

Logistic regression was performed to control for confounders that were significantly different at the $p < 0.05$ level between the compared groups using chi-square test or Fisher's exact test. Adjusted odds ratio (OR) and 95% confidence intervals (CI) were calculated for each ratio group, with the highest ratio group (aPLT:PRBC $\geq$ 1:6) set as the reference cohort (OR 1.0).

A Cox regression model was used to further evaluate the association between the aPLT:PRBC ratio and mortality, treating the aPLT:PRBC ratio as a time-dependent covariate. This analysis allowed examination of the relationship between in-hospital mortality and the aPLT:PRBC ratio over time, taking into account the fact that patients might have transitioned between the ratio groups at each time interval of interest (2-hour intervals from admission to 24 hours postadmission).

In addition, in order to determine if the aPLT:PRBC ratio was independently associated with mortality, a stepwise logistic regression model was performed including all factors that had a $p < 0.2$ from the univariate analysis.

Values are reported as means $\pm$ standard deviation (SD) for continuous variables and as percentages for categorical variables. All analyses were performed using the Statistical Package for Social Sciences (SPSS Windows), version 12.0 (SPSS Inc).

RESULTS

During the 9-year study period, 5,872 (18.2%) of the 32,289 injured patients admitted to this center received a blood transfusion. A total of 657 (11.2%) of these patients required an MT. At 24 hours after admission, a total of 171 patients (26.0%) received a low ratio, 77 patients (11.7%) a medium ratio, 249 patients (37.9%) a high ratio, and 160 patients (24.4%) the highest ratio of aPLT:PRBC. No statistically significant change in the incidence of the different aPLT:PRBC ratios were observed over the 9-year study period. The platelet transfusion was front loaded, with 64.1% of all aPLT units transfused within the first 24 hours being given within the first 6 hours after admission. This was constant throughout all 4 groups, with 77.8%, 58.3%, 68.4%, and 59.9% of the aPLT units being given within the first 6 hours in the low, medium, high and highest ratio groups, respectively. The average age of these patients was 34.9 $\pm$ 17.0 years and the mean ISS was 28.7 $\pm$ 14.5. Detailed demographic and clinical injury characteristics of the study groups are described in Table 1. Table 2 depicts the summary of blood components used for resuscitation during the initial 24 hours stratified by platelet ratio groups. These, along with the differences in demographic and clinical injury data, were corrected for in the logistic regression.

Table 1. Demographic and Clinical Injury Characteristics of All Massively Transfused Patients Stratified by Platelet Ratio

Characteristic	Total (n = 657)	Low ratio (n = 171)	Medium ratio (n = 77)	High ratio (n = 249)	Highest ratio (n = 160)	p Value
Age ≥ 55 y, % (n)	12.6 (83/657)	11.7 (20/171)	11.7 (9/77)	12.9 (32/249)	13.8 (22/160)	0.942
Male, % (n)	83.6 (549/657)	86.0 (147/171)	87.0 (67/77)	80.7 (201/249)	83.8 (134/160)	0.415
Penetrating, % (n)	54.8 (360/657)	53.8 (92/171)	58.4 (45/77)	55.4 (138/249)	53.1 (85/160)	0.873
SBP < 90 mmHg, % (n)	31.4 (199/633)	40.2 (66/164)	18.9 (14/74)	33.2 (80/241)	25.3 (39/154)	0.003
GCS ≤ 8, % (n)	31.6 (205/649)	44.8 (74/165)	27.3 (21/77)	27.8 (69/248)	25.8 (41/159)	<0.001
ISS, mean ± SD	28.7 ± 14.5	29.9 ± 16.1	27.3 ± 12.6	28.7 ± 14.6	28.1 ± 13.3	0.545
ISS ≥ 25, % (n)	64.4 (423/657)	64.3 (110/171)	62.3 (48/77)	65.1 (162/249)	64.4 (103/160)	0.979
Head AIS ≥ 3, % (n)	21.5 (141/657)	21.1 (36/171)	22.1 (17/77)	18.5 (46/249)	26.3 (42/160)	0.317
Chest AIS ≥ 3, % (n)	51.1 (336/657)	50.9 (87/171)	42.9 (33/77)	52.2 (130/249)	53.8 (86/160)	0.446
Abdomen AIS ≥ 3, % (n)	63.0 (414/657)	62.0 (106/171)	59.7 (46/77)	68.3 (170/249)	57.5 (92/160)	0.140
Extremity AIS ≥ 3, % (n)	36.5 (240/657)	37.4 (64/171)	40.3 (31/77)	34.9 (87/249)	36.3 (58/160)	0.850

AIS, Abbreviated Injury Score; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; SBP, systolic blood pressure; SD, standard deviation.

Mortality was examined at 12 and 24 hours and is illustrated in Figures 1 and 2, respectively. At 12 hours, the overall mortality was 32.7% (n = 215). A stepwise increase in adjusted mortality with decreasing platelet ratio was observed at this time point. Using the highest ratio group as the reference group, the adjusted (adj.) relative risk of death was 1.77 (95% CI 0.99 to 3.17; adj. p = 0.054) for the high ratio group, 2.44 (95% CI 1.13 to 5.26; adj. p = 0.023) for the medium ratio group, and 3.75 (95% CI 1.88 to 7.45; adj. p < 0.001) for the low ratio group (Fig. 1). At 24 hours, the overall mortality was 36.7% (n = 241), increasing in a similar stepwise fashion with decreasing aPLT:PRBC ratio. The adjusted relative risk of death was 1.67 (95% CI 0.99 to 2.82; adj. p = 0.054) for the high ratio group, 2.28 (95% CI 1.19 to 4.39; adj. p = 0.013) for the medium ratio group, and 5.51 (95% CI 2.76 to 10.98; adj. p < 0.001) for the low ratio group (Fig. 2). For overall survival to discharge, as the platelet ratio increased, a stepwise decrease in mortality was seen, from 72.1% to 33.1% (adj. p < 0.001).

Subsequently, the Cox regression analysis was performed using the aPLT:PRBC ratio as a time-dependent covariate. A decreasing aPLT:PRBC ratio was significantly associated with increasing mortality (adj. p = 0.007, OR [95% CI] 1.87 [1.18 to 2.97], adjusted for FFP:PRBC ratio [%], cryoprecipitate, hypotension on admission [<90 mmHg vs ≥90mmHg], and GCS on admission [≤8 vs >8]).

After univariate analysis, the risk factors associated with mortality at 24 hours were identified (Table 3). These factors were used in addition to the aPLT:PRBC ratio, the FFP:PRBC ratio, and the PRBC units transfused within 24 hours to build a stepwise logistic regression model to identify independent predictors of mortality at 24 hours. Variables independently associated with increased mortality included a GCS ≤ 8, PRBC units transfused within 24 hours, hypotension on admission, and an ISS ≥ 25. Variables independently associated with improved survival at 24 hours included the FFP:PRBC ratio and the aPLT:PRBC ratio. The R^2 for this regression model was 0.54 (Table 4).

DISCUSSION

For acutely injured patients surviving to hospital, the primary cause of preventable death is uncontrolled blood loss.[21-23] For these patients requiring an MT, defined in most research protocols as ≥10 units of PRBC within the first 6 to 24 hours, the aggressive early use of plasma has been widely applied as the central component of a damage control resuscitation strategy. Although not universally

Table 2. Blood Component Summary for the First 24 Hours Stratified by Platelet Ratio

Variable	Total (n = 657)	Low ratio (n = 171)	Medium ratio (n = 77)	High ratio (n = 249)	Highest ratio (n = 160)	p Value
PRBC, U, mean ± SD	18.0 ± 9.8	15.5 ± 6.6	19.7 ± 10.6	20.5 ± 12.1	15.8 ± 6.7	<0.001
FFP, U, mean ± SD	8.6 ± 7.3	5.1 ± 5.5	9.4 ± 9.0	10.3 ± 8.1	9.2 ± 5.3	<0.001
aPLT, U, mean ± SD	1.9 ± 1.7	0.2 ± 0.4	1.3 ± 0.8	2.4 ± 1.5	3.4 ± 1.5	<0.001
FFP:PRBC ratio. %, mean ± SD*	48.2 ± 31.7	34.0 ± 37.0	46.2 ± 26.7	51.0 ± 26.8	60.1 ± 29.2	<0.001
Cryoprecipitate, U, mean ± SD	4.9 ± 8.7	2.0 ± 5.1	4.8 ± 7.6	6.6 ± 9.9	5.5 ± 9.6	<0.001

*FFP:PRBC ratio (%) = (units FFP/units PRBC) × 100.
aPLT, apheresis platelets; FFP, fresh frozen plasma; PRBC, packed red blood cells.

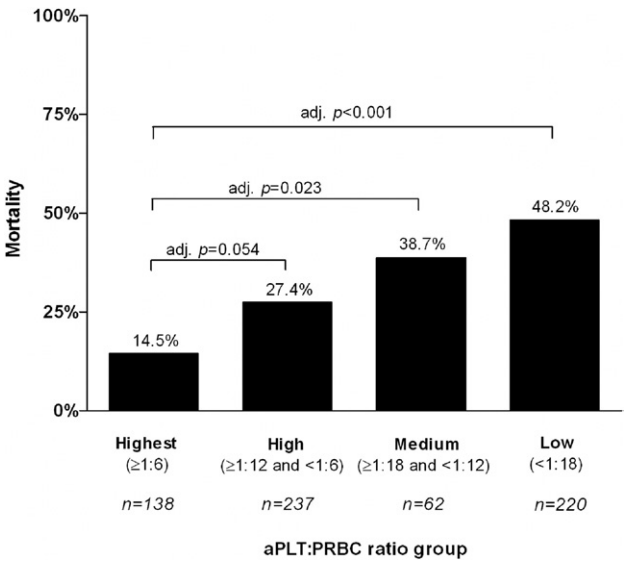

Figure 1. Mortality for massively transfused patients at 12 hours stratified by platelet ratio. Adjusted for GCS on admission (≤8 versus >8), FFP:PRBC ratio (%) at 12 h, cryoprecipitate at 12 h. adj, adjusted; aPLT, apheresis platelets; FFP, fresh frozen plasma; GCS, Glasgow Coma Scale; PRBC, packed red blood cells.

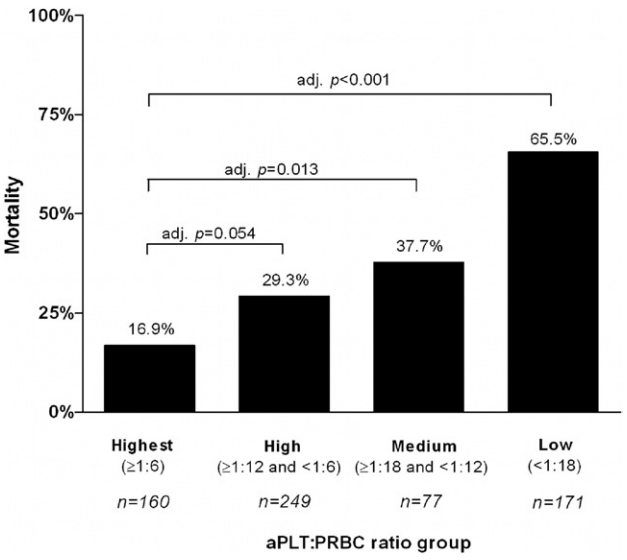

Figure 2. Mortality for massively transfused patients at 24 hours stratified by platelet ratio. Adjusted for hypotension on admission (<90 mmHg versus ≥90 mmHg), GCS on admission (≤8 versus >8), FFP:PRBC ratio (%) at 24 h, cryoprecipitate at 24 h.adj, adjusted; aPLT, apheresis platelets; FFP, fresh frozen plasma; GCS, Glasgow Coma Scale; PRBC, packed red blood cells.

supported,[24-26] the bulk of the evidence from both military[6-8] and civilian[9-17] centers, including the recently published multicenter study by Holcomb and colleagues[10] incorporating data from 16 civilian Level I trauma centers, demonstrates that a survival advantage is conferred by the aggressive use of plasma in ratios approaching 1:1.

For platelets, however, the evidence is less clear.[10 13,18-20,27] One of the earliest attempts to quantitate the impact of platelets in MT was performed by Cinat and associates.[19] Although limited by their definition of an MT (>50 units in 48 hours), and the inclusion of whole blood and component red cells as well as pooled and apheresis platelets, they showed that survivors received a higher platelet ratio of 1:7.7 as compared with 1:11.9 for nonsurvivors. In a subsequent before-and-after study by Gunter and coauthors,[20] 63 patients undergoing MT who received platelets at a ratio of ≥1:5 had a lower mortality than a comparison group receiving a ratio of <1:5 (38% vs 61%, p = 0.001). Data extracted from 462 penetrating combat casualties treated in Baghdad demonstrated similar results.[18] Stratified by platelet ratios, there was a stepwise increase in survival with increasing platelet transfusion from a low of 64% with a ratio of <1:16 to upwards of 95% for ratios exceeding 1:8. The aPLT:PRBC ratio was independently associated with survival at both 24 hours and 30 days. Finally, in the multicenter study by Holcomb and associates,[10] a practical approach to this question was taken by grouping patients according to both their plasma and platelet ratios. Patients receiving a combination of high plasma and high platelets had improved 6-hour, 24-hour, and 30-day survival.

In our study, increasing platelet transfusion, in ratios approaching 1:6, was associated with a stepwise improvement in survival at 12 and 24 hours and in overall survival to discharge. With each apheresis unit equivalent to approximately 6 random donor units, this represents an optimal ratio of 1:1 for random platelets:PRBC. The aPLT:PRBC ratio was also found to be independently associated with improved survival.

The role of platelets in the acute resuscitation of critically ill trauma patients has undergone change as our transfusion protocols have evolved. In the era of stored whole blood transfusion, one of the earliest defects seen after massive transfusion was a deficit in the functional platelet concentration.[28-31] When stored in whole blood at 4°C, these highly temperature-sensitive platelets rapidly became dysfunctional and were quickly cleared from the systemic circulation. Clotting factors, however, with the possible exception of factors V and VIII, were well retained in stored whole blood. With the North American red cell replacement standard changing to component therapy, these clotting factors also became depleted in patients requiring massive transfusions of factor-poor PRBC units. When comparing the impact of the platelet deficit with plasma, it appears that plasma exerts a stronger effect on mortality than platelets. In Hirshberg and coworkers,[32] computer modeling simulation of massive transfusion, prolongation

Table 3. Risk Factors for Mortality at 24 Hours for Massively Transfused Patients

Variable	Mortality at 24 h, %	n	p Value	Odds ratio (95% CI)
Gender				
Male	37.3	205/549	0.430	1.19 (0.77–1.84)
Female	33.3	36/108		
Mechanism				
Penetrating	40.6	146/360	0.023	1.45 (1.05–2.00)
Blunt	32.0	95/297		
Age, y				
≥ 55	32.5	27/83	0.401	0.81 (0.50–1.32)
< 55	37.3	214/574		
SBP, mmHg				
< 90	55.3	110/199	<0.001	3.16 (2.23–4.48)
≥ 90	28.1	122/434		
GCS				
≥ 8	63.9	131/205	<0.001	5.72 (3.99–8.19)
> 8	23.6	105/444		
ISS				
≥ 25	43.5	184/423	<0.001	2.39 (1.68–3.41)
< 25	24.4	57/234		
AIS Head				
≥ 3	37.6	53/141	0.801	1.05 (0.72–1.54)
< 3	36.4	188/516		
AIS Chest				
≥ 3	41.4	139/336	0.011	1.52 (1.10–2.09)
< 3	31.8	102/321		
AIS Abdomen				
≥ 3	40.3	167/414	0.011	1.54 (1.10–2.16)
< 3	30.5	74/243		
AIS Extremity				
≥ 3	32.1	77/240	0.064	0.72 (0.52–1.02)
< 3	39.3	164/417		

AIS, Abbreviated Injury Score; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; SBP, systolic blood pressure.

of the prothrombin time was demonstrated to be the primary defect seen, followed later by a platelet deficit. They suggested that the dilution of platelets is not only slower, but likely more variable as well, due to individual variation in consumption and endogenous recruitment. In our regression, the R^2 value for FFP:PRBC ratio was 0.269 compared with 0.035 for aPLT:PRBC. This would suggest that of the 2, the primary focus during the acute resuscitation phase should be on plasma replacement. In fact, in a randomized controlled trial by Reed and colleagues[33] evaluating pooled platelet transfusion at a ratio of 1:2 versus plasma in patients receiving ≥12 units of whole blood in 12 hours, the conclusion was that platelet administration did not affect microvascular nonsurgical bleeding. This study, although small, using only whole blood and achieving only a ratio of 1:2, is important because it is the only prospective randomized data available and supports the primary importance of plasma in these patients who have microvascular nonsurgical bleeding.

This study is limited by its retrospective study design. The errors inherent in any trauma registry, in particular, with respect to blood component transfusion, have been highlighted in our previous studies.[12,34] Attempts have been made to mitigate this by using transfusion data abstracted exclusively from the blood bank, where dispensing and use data is stringently regulated by the US Food and Drug Administration (FDA). These regulations mandate that all blood banks maintain comprehensive records for each unit dispensed, and it is hoped that this minimized the errors associated with this retrospective analysis.

In the evidence base addressing the impact on survival of component replacement for acute resuscitation, there has been inconsistency in the exclusion of early deaths. In the analysis by Snyder and associates,[24] the "survival bias" was examined as a potential confounding signal that may categorize patients who survived to receive plasma as patients who survived because they received plasma. This is of particular concern in the evaluation of treatment effects on populations with a high rate of early deaths and a significant delay to initiation of treatment. We analyzed our results with the exclusion of deaths in the emergency department as well as those at 24 hours; however, the conclusions remained the same. In addition, our analysis of the timing of platelet transfusion showed that they were heavily front loaded and that a consistent proportion of the total 24-hour platelet load was administered within the first 6 hours across all groups. Furthermore, the "survival bias" was addressed by using the aPLT:PRBC ratio as a time-dependent covariate in the regression model. These results demonstrated again that with decreasing aPLT:PRBC ratios, mortality significantly increased.

This study did not provide any insight into which patients would go on to require an MT and therefore benefit from aggressive platelet use. In the wider application of these results, defining the predictors of the need for an MT will remain a critical goal for future studies.

Data regarding platelet function was also not available for analysis. Renal failure, liver dysfunction, and the presence of antiplatelet agents could not be accurately determined. The negative impact of hypothermia and acidosis on platelet function likewise could not be quantified. Platelet function analyzer data was also not available throughout the duration of the study. Although plasma and cryoprecipitate data were accurately captured and adjusted for, the

Table 4. Predictors of Mortality at 24 Hours

Step	Variable	Adjusted odds ratio (95% CI)	Adjusted p value	R^2
1	FFP:PRBC ratio (%) at 24 h*	0.96 (0.95–0.97)	<0.001	0.269
2	GCS ≤ 8	6.57 (3.98–10.86)	<0.001	0.167
3	PRBC units within 24 h	1.06 (1.04–1.08)	<0.001	0.041
4	aPLT:PRBC ratio (%) at 24 h†	0.92 (0.89–0.95)	<0.001	0.035
5	SBP < 90 mmHg	2.42 (1.49–3.95)	<0.001	0.016
6	ISS ≥ 25	2.05 (1.27–3.32)	0.003	0.012

Regression included variables with $p < 0.2$ on univariate analysis. The FFP:PRBC ratio (%) at 24 h, the aPLT:PRBC ratio (%) at 24 h, and the PRBC units transfused within 24 h were forced into the regression model.
*FFP:PRBC ratio (%) = (units FFP/units PRBC) × 100.
†aPLT:PRBC ratio (%) = (units aPLT/units PRBC) × 100.
aPLT, apheresis platelets; FFP, fresh frozen plasma; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; PRBC, packed red blood cells; SBP, systolic blood pressure.

procoagulant effects of agents such as factor VIIa could not be accurately abstracted. Consequently, clear data on the functional coagulation status of these patients and its temporal association with platelet transfusion could not be analyzed.

Despite these limitations, this is the largest study to date examining the impact of apheresis platelet transfusion in patients undergoing an MT. In this study, there was a stepwise improvement in survival with increasing platelet-to-PRBC ratios. The ratio of apheresis platelets to blood was independently associated with survival.

In conclusion, for injured patients requiring a massive transfusion, as the apheresis platelet-to-red cell ratio approached 1:6, a stepwise improvement in survival was seen. The magnitude of the impact exerted by platelets on survival was not as strong as that of plasma transfusion. However, further prospective evaluation of the optimal platelet ratio and trigger for transfusion in patients undergoing a massive transfusion is warranted.

Author Contributions

Study conception and design: Inaba, Demetriades, Rhee
Acquisition of data: Lustenberger, Shulman, Nelson, Talving
Analysis and interpretation of data: Inaba, Lustenberger, Rhee, Holcomb, Blackbourne, Shulman, Nelson, Talving, Demetriades
Drafting of manuscript: Inaba, Lustenberger
Critical revision: Inaba, Lustenberger, Rhee, Holcomb, Blackbourne, Shulman, Nelson, Talving, Demetriades

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