European Journal of Trauma and Emergency Surgery (2019) 45:671–679
https://doi.org/10.1007/s00068-018-0953-4

ORIGINAL ARTICLE

Platelet transfusion increases risk for acute respiratory distress syndrome in non-massively transfused blunt trauma patients

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Received: 13 February 2018 / Accepted: 3 April 2018 / Published online: 7 April 2018

Abstract

Purpose While damage control resuscitation is known to confer a survival advantage in severely injured patients, high-ratio blood component therapy should be initiated only in carefully selected trauma patients, due to the morbidity associated with blood product use. With this project, we aim to identify the effect of platelet transfusion in non-massively transfused bluntly injured patients.

Methods The Glue Grant database was retrospectively queried and severely injured blunt trauma patients who underwent non-massive transfusion were identified. Patients were divided into quartiles depending on platelet volume they were transfused in the first 48 h. Outcomes of interest included mortality; ventilator, Intensive Care Unit (ICU) and hospital length of stay (LOS); infectious and non-infectious complications. Multivariable regression models were fitted for these outcomes, controlling for age, pre-existing comorbidities, injury severity, acute physiologic derangement, neurologic injury burden, and other fluid and blood product resuscitation.

Results There was no difference in mortality, LOS, or the incidence of multi-organ failure and infectious complications. However, patients receiving ≥ 250 mL of platelets were more likely to develop acute respiratory distress syndrome (ARDS) compared to those who received < 250 mL [odds ratio 1.91 (95% CI 1.10–3.33, $p = 0.022$)].

Conclusions Pre-emptive platelet transfusion should be avoided in non-massively transfused blunt injury victims in the absence of true or functional thrombocytopenia, as it increases risk for ARDS with no survival benefit.

Keywords Blunt trauma · Platelets · Transfusion · Glue Grant · Acute lung injury/acute respiratory distress syndrome

Introduction

Unintentional injury is the leading cause of death in individuals aged 1–44 in the United States [1] and one of the leading causes of death and disability worldwide [2]. The majority of trauma-related mortality is secondary to hemorrhage and coagulopathy [3]. The early administration of blood products in a composition similar to that of whole blood, namely packed red blood cells (PRBC), fresh frozen plasma (FFP), and platelets (PLT) in ratios approximating

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1:1:1, has been shown to confer a survival advantage in patients with severe trauma who require massive transfusion (MT) (defined as requirement of > 10 PRBC units in the first 6–24 h (h) post injury) [4, 5]. These findings have led to the institution of MT protocols at military and civilian trauma centers worldwide with significant gains in post-injury survival [6].

While it would be technically feasible to initiate such high-ratio transfusion therapy early on in all patients with acute traumatic bleeding, such a practice would not be without significant risks: Allergic, inflammatory and infectious complications are well described side effects of component therapy [7]. The additional risk of such complications is acceptable in the massively transfused trauma population, as the survival benefit of MT outweighs the risk of post-transfusion sequelae. However, it is difficult to predict early in the resuscitative process what subset of trauma patients will end up requiring MT, as operative interventions, and more recently, interventional radiology can help control the bleeding [8].

Additionally, while blood products have been associated with prolonged mechanical ventilation [9–11]; longer intensive care unit (ICU) [9–11] and hospital length of stays (LOS) [9]; and greater incidence of ventilator-associated pneumonias (VAP) [12], acute respiratory distress syndrome (ARDS) [13, 14], transfusion-related acute lung injury (TRALI) [15], and multiple organ failure (MOF) [14, 16] in injured victims, the effect of PLT transfusion is less clearly defined. Sambasivan and colleagues recently demonstrated that non-massively transfused (NMT) trauma patients receiving a high ratio of PLT:PRBC (> 1:2) had significantly decreased ventilator-free and ICU-free days compared to their low ratio counterparts [11]. However, this study did not account for the amount of crystalloid infused in the early resuscitative period, a factor increasingly identified to be associated with such outcomes [17, 18], and the impact of PLT on inflammatory and infectious complications was not assessed.

With this study, we aim to determine if a relationship exists between platelet transfusion in NMT blunt trauma patients and clinically relevant outcomes.

Methods

Data collection

Data were derived from a multicenter prospective cohort of severely injured blunt trauma patients with clinically significant hemorrhage, the Glue Grant (National Institute of General Medical Sciences, Inflammation and the Host Response to Injury Collaborative Program, http://www.gluegrant.com). Institutional Review Board approval was obtained from each of the participating institutions during subject enrolment.

For eligible patients, demographic, laboratory and clinical data, including volume of crystalloid, colloid and blood products administered, were collected. Standardized protocols were developed and implemented at all participating study institutions to provide guidelines for resuscitation and blood product transfusion; sedation/analgesia and mechanical ventilation; VAP diagnosis and treatment; glucose control; and thromboembolic event prophylaxis. Parameters of MOF of various systems including renal, hepatic, cardiac, metabolic, hematologic, and neurologic systems were determined daily. The emergence of infectious [surgical site infection (SSI), bloodstream infections (BSI) and VAP and non-infectious complications (ARDS and MOF)] was recorded daily. After compilation and validation, de-identified data were incorporated into the Glue Grant database and made available for secondary analysis to approved investigators.

Inclusion and exclusion criteria

Enrollment criteria for the Glue Grant study include a blunt mechanism of injury, evidence of significant pre-hospital hemorrhage, in the absence of severe central nervous system injury. Trauma patients aged < 16 and > 90 years, or who arrived at the ED more than 6 h after injury were excluded. Patients expected to live less than 24 h due to their injury, or less than 28 days due to another medical condition were excluded to minimize survival bias. Inability to obtain first blood draw within 12 h or to obtain informed consent either directly or via a healthcare proxy also led to exclusion.

For our analysis, subjects who received massive transfusion (defined here as having received > 10 units of PRBCs in the first 12 h) did not receive any PLT or expired in the first 48 h, were excluded (as they would not live long enough to develop transfusion-related sequelae).

Definition of complications

The diagnosis of MOF required a Marshall Multiple Organ Dysfunction score of > 5 [19]. Definitions of the aforementioned outcomes, namely ARDS, VAP, as well as BSI and SSI have been described extensively elsewhere [19].

Outcomes and hypothesis

Our primary outcome was PLT transfusion-related mortality. Secondary outcomes included time on mechanical ventilation, ICU and hospital LOS, infectious (VAP, BSI, SSI) and non-infectious (MOF, ARDS) complications. Our hypothesis was that platelet transfusion in NMT blunt trauma patients does not affect mortality, or any of our secondary outcomes.

Statistical analysis

The study population was assessed for differences in mortality and our secondary outcomes based on the amount of platelet transfusion in the first 48 h after injury. To simplify analysis, blood product volumes were converted from raw data in milliliters to clinically relevant units per the following conversion scheme: 1 unit PRBC = 350 mL, 1 unit FFP or 1 apheresis unit PLT = 250 mL, 1 unit cryoprecipitate = 60 mL. Summary statistics are presented as means ± standard deviations or medians (interquartile ranges) for normally and not-normally distributed variables, respectively.

Patients were grouped into quartiles depending on the volume of PLT therapy they received, and Mantel–Haenszel tests of trend were performed across the characteristics of the four groups. Multivariate logistic and linear regression analyses of our binary and continuous outcome measures were fitted, respectively, adjusting for age, severity of physiologic derangement (by APACHE II score), injury burden [by Injury Severity Score (ISS)], comorbidities (by Charlson Comorbidity Index), pre-hospital GCS, infused crystalloids and colloids, as well as transfused blood products in the first 48 h post injury, and the adjusted Odds Ratios were calculated across the 4 quartiles of PLT volume administration and graphically represented. Polynomial (for the platelet volume) and interaction terms (platelet volume against plasma and packed red blood cells) were also included in the analysis as needed, and remained in the model if improved model fit or found to be statistically significant. The same analyses were also performed comparing subjects that received < 250 mL of PLT (the lowest volume quartile) versus those that received more.

For the logistic regression models, post-estimation Pearson goodness-of-fit tests were obtained. For the linear regression models, residuals were assessed for outliers and influential values, using leverage and standardized residuals, and the areas under the curve were calculated for model fit. Observations with outlying and highly influential residuals were left in our sample as true outliers, if data collection was deemed correct. Adjusted odds ratios are reported for binary outcome variables for each of the four quartiles (or the patients receiving ≥ 250 mL of PLT), with the group having received < 250 mL of PLT as the reference. All statistical analyses were performed in Stata 13.1 (StataCorp, College Station, TX).

Results

Out of 2002 blunt trauma patients enrolled in the Glue Grant cohort, a total of 1465 were excluded for a sample size of $n = 488$ (Fig. 1). The demographics, laboratory and clinical characteristics of our sample population are summarized in Table 1. Overall, the population was young (age 43.7 ± 19.9), male (65.6%), relatively healthy [CCI 0 (0–1)] and did not have significant neurologic injury rehospital GCS 14 [7–15]. Patients were severely injured (ISS 33.2 ± 13.0) with 71% having an ISS > 25. 26 patients (5.33%) were on antiplatelet therapy at baseline (before the traumatic event).

Comparing patients across the four PLT volume quartiles, volume of PLT administration increased as APACHE

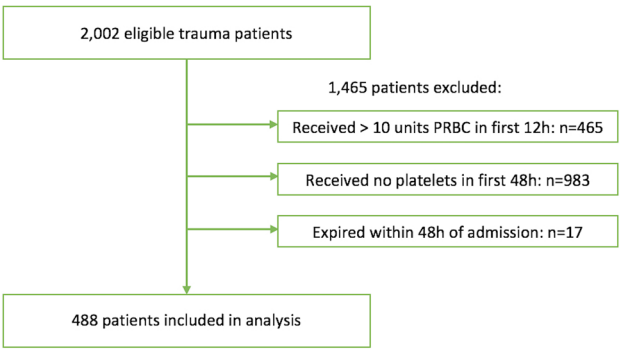

Fig. 1 Flow diagram of our study population

Table 1 Demographics, laboratory and clinical characteristics of our sample population

	Total ($n = 488$)
Age (year)	43.7 ± 19.9
Male sex (%)	65.6
ED SBP (mmHg)	111 ± 30.6
I ED HR (min^{-1})	109.7 ± 25.9
GCS at scene	14 (7–15)
WBC	16.3 ± 7.5
Admission Hb (g/dL)	11 ± 2.5
Base deficit	− 8.1 ± 4.2
Lactate (mmol/L)	4 (2.6–5.8)
APACHE II	29.3 ± 6.1
ISS	33.2 ± 13.0
ISS > 25 (%)	70.9
Charlson Comorbidity Index	0 (0–1)
Major surgery in first 24 h (%)	31.9
Ventilator days (day)	8 (4–14)
ICU LOS (day)	11 (6–18)
Hospital LOS (day)	21 (13–31)
Mortality (%)	8.6

Normally distributed values are summarized as means ± standard deviations, not-normally distributed values as medians and interquartile ranges, and binary variables as percentages

SD standard deviation; *ED* emergency department; *SBP* systolic blood pressure; *HR* heart rate; *GCS* Scene Glasgow Coma Scale; *WBC* white blood cell count; *Hb* hemoglobin; *BD* base deficit; *APACHE II* Acute Physiology and Chronic Health Evaluation II Score; *ISS* Injury Severity Score; *ICU* Intensive Care Unit; *LOS* length of stay

and CCI increased ($p = 0.018$ and $p = 0.011$, respectively, Table 2). Interestingly, there was no difference across quartile groups with regard to number of patients on antiplatelet therapy at baseline ($p = 0.929$). Not surprisingly, patients who received greater volumes of PLT product had longer ventilator ($p = 0.001$), ICU ($p = 0.001$) and overall hospital stays ($p = 0.026$), likely because they also received larger volumes of fluids (crystalloids and colloids) and other blood products. ($p = 0.012$ and $p < 0.001$, respectively, Table 2). As a result of the greater volumes of resuscitation with crystalloid and blood products, and perhaps of the greater physiologic derangement, patients receiving larger volumes of PLT therapy demonstrated a higher incidence of ARDS ($p = 0.019$), MOF ($p = 0.001$), and overall non-infectious complications ($p = 0.017$), while there was no mortality difference ($p = 0.173$). Similarly, there was no difference in VAP ($p = 0.484$), BSI ($p = 0.608$), SSI ($p = 0.366$) or overall nosocomial infectious complication rate ($p = 0.216$). Age ($p = 0.183$), pre-hospital GCS ($p = 0.907$), hemodynamic (ED SBP, $p = 0.599$ and ED HR, $p = 0.187$) and initial hemoglobin levels ($p = 0.198$), as well as injury severity ($p = 0.349$) did not differ across groups.

Examining the adjusted Odds Ratios/beta-coefficients for our outcome measures, patients that received ≥ 250 mL of PLT were not at greatest risk for mortality; prolonged ventilation, ICU or hospital length of stay; or to develop MOF, VAP, SSI, nosocomial infections or non-infectious complications compared to their counterparts that received < 250 mL of PLT (Table 3; Fig. 2). Their risk, however, of developing ARDS was greater than twofold if they received 250–300 mL [O.R. 2.30 (95% CI 1.21–4.35), $p = 0.011$] or > 540 mL [O.R. 2.07 (95% CI 1.04–4.12), $p = 0.038$]. This risk was independently attributed to greater PLT use, and was noted regardless of the subjects' age, APACHE II score, injury severity and comorbidities, GCS and volume of infused crystalloids, colloids, and other blood products. This finding persisted even when the large volume (≥ 250 mL) PLT recipients were compared against the low volume (< 250 mL) [O.R. 1.91 (95% CI 1.10–3.33), $p = 0.022$] (Table 4). This finding suggests that PLT administration is an independent risk factor for the development of ARDS in

Table 2 Distribution of injury severity across platelet volume quartiles and dose-dependent effect of platelet transfusion on morbidity

48-h volume of transfused platelets	< 250 mL	250–300 mL	301–540 mL	> 540 mL	*p* value
n =	125	139	107	117	
Age	41.5 ± 19.8	44.9 ± 20.0	42.2 ± 19.5	46.0 ± 20.2	0.183
GCS	11.0 ± 4.7	11.4 ± 4.8	11.6 ± 4.4	10.7 ± 4.9	0.907
ED SBP (mmHg)	106.1 ± 28.4	119.4 ± 31.6	110.0 ± 26.5	107.2 ± 33.3	0.599
ED HR (min^{-1})	112.5 ± 25.1	110.0 ± 25.8	109.1 ± 25.1	107.1 ± 27.7	0.187
BD	− 8.9 ± 4.2	− 7.8 ± 3.9	− 8.1 ± 4.2	− 7.5 ± 4.5	**0.016**
Hb (g/dL)	11.1 ± 2.5	10.9 ± 2.4	11.3 ± 2.6	10.6 ± 2.5	0.198
ISS	34.2 ± 14.0	32.1 ± 12.7	34.7 ± 13.1	32.0 ± 12.2	0.349
APACHE II	28.6 ± 6.5	28.7 ± 5.9	29.4 ± 5.3	30.8 ± 6.5	**0.018**
Comorbidity index	0.4 ± 0.9	0.4 ± 1.0	0.4 ± 0.9	0.8 ± 1.6	**0.011**
Crystalloid volume over 48 h (L)	17.6 ± 6.9	16.4 ± 7.3	19.4 ± 8.2	19.7 ± 9.7	**0.012**
Colloid volume over 48 h (L)	0.2 ± 0.5	0.3 ± 0.8	0.4 ± 0.7	0.4 ± 0.8	0.084
Blood product volume over 48 h (L)	3.7 ± 1.7	3.7 ± 1.5	5.0 ± 2.0	6.3 ± 2.8	**< 0.001**
% on antiplatelet therapy	4.8	6.5	3.7	6.0	0.929
Mortality (%)	8	6.5	7.5	12.8	0.173
Ventilator days	9.8 ± 9.6	9.8 ± 8.3	10.6 ± 8.4	12.6 ± 11.0	**0.001**
ICU LOS	13.4 ± 12.4	13.2 ± 10.7	13.8 ± 9.0	15.8 ± 11.4	**0.001**
Hospital LOS	24.0 ± 9.9	24.6 ± 16.4	26.0 ± 21.0	27.6 ± 20.7	**0.026**
ARDS (%)	19.2	30.9	26.2	35.0	**0.019**
MOF (%)	27.2	27.3	29.0	47.0	**0.001**
VAP (%)	28.8	34.5	31.8	34.2	0.484
BSI (%)	17.6	7.2	9.3	14.5	0.608
SSI (%)	11.3	15.1	13.1	16.2	0.366
Non-infectious complications	41.1	48.9	43.9	59.0	**0.017**
Nosocomial infections (%)	48.4	54.7	53.3	57.3	0.216

GCS Scene Glasgow Coma Scale; *ED* emergency department; *SBP* systolic blood pressure; *HR* heart rate; *ISS* Injury Severity Score; *APACHE II* Acute Physiology and Chronic Health Evaluation II Score; *ICU* Intensive Care Unit; *LOS* length of stay; *ARDS* acute respiratory distress syndrome; *MOF* multiple organ failure; *VAP* ventilator-associated pneumonia; *BSI* bloodstream infection; *SSI* surgical site infection

Table 3 Adjusted Odds Ratios/beta-coefficients for clinically relevant outcomes, controlling for age, pre-hospital Glasgow Coma Scale, Injury Severity and APACHE II scores, comorbidities, crystalloid, colloid and blood product administration over the same time frame

PLT volume	< 250 mL	250–300 mL		301–540 mL		> 540 mL	
			p		*p*		*p*
Mortality	Reference	0.97 (0.34 to 2.71)	0.946	1.13 (0.39 to 3.3)	0.822	1.76 (0.64 to 4.84)	0.272
ICU LOS	Reference	− 0.13 (− 2.59 to 2.34)	0.919	− 0.89 (− 3.52 to 1.75)	0.509	0.12 (− 2.60 to 2.83)	0.933
Hospital LOS	Reference	1.14 (− 3.50 to 5.78)	0.630	− 0.21 (− 5.18 to 4.75)	0.932	− 0.03 (− 5.13 to 5.08)	0.992
Ventilator days	Reference	0.21 (− 1.89 to 2.32)	0.842	0.04 (− 2.20 to 2.29)	0.971	1.25 (− 1.06 to 3.56)	0.289
ARDS	Reference	2.30 (1.21 to 4.35)	**0.011**	1.39 (0.70 to 2.75)	0.341	2.07 (1.04 to 4.12)	**0.038**
MOF	Reference	0.96 (0.53 to 1.75)	0.904	0.79 (0.42 to 1.48)	0.466	1.63 (0.87 to 3.02)	0.125
VAP	Reference	1.41 (0.79 to 2.50)	0.247	1.06 (0.57 to 1.96)	0.850	0.99 (0.52 to 1.87)	0.974
BSI	Reference	0.42 (0.18 to 1.01)	0.052	0.46 (0.20 to 1.10)	0.074	0.62 (0.28 to 1.39)	0.251
SSI	Reference	1.56 (0.72 to 3.39)	0.256	1.04 (0.45 to 2.41)	0.920	1.27 (0.55 to 2.91)	0.580
Non to infectious complications	Reference	1.57 (0.92 to 2.66)	0.098	0.93 (0.53 to 1.65)	0.809	1.47 (0.82 to 2.63)	0.198
Nosocomial infections	Reference	1.37 (0.80 to 2.34)	0.248	1.11 (0.63 to 1.96)	0.717	1.11 (0.61 to 2.00)	0.734

O.R. odds ratios; *95% CI* 95% confidence intervals; *ICU LOS* Intensive care unit length of stay; *ARDS* acute respiratory distress syndrome; *VAP* ventilator-associated pneumonia; *MOF* multiple organ failure; *BSI* bloodstream infection; *SSI* surgical site infection

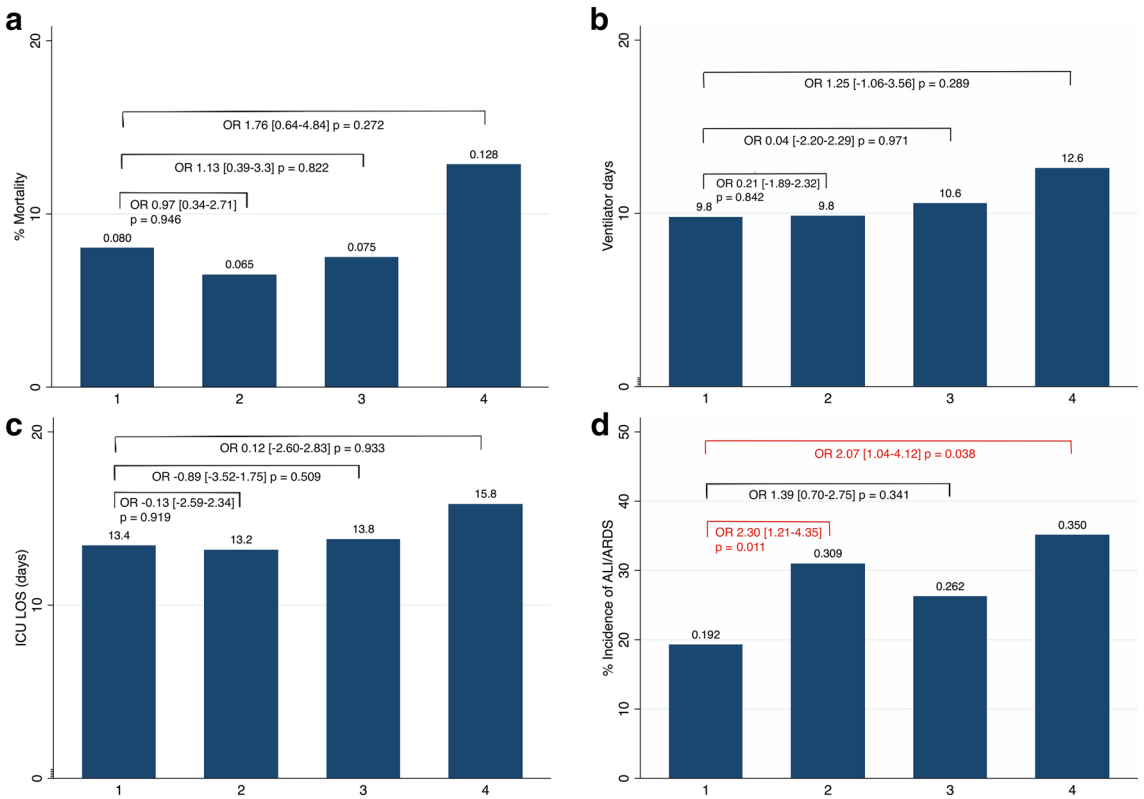

Fig. 2 Vertical bars represent unadjusted incidence of complications or length of stay (**a** mortality; **b** ventilation duration; **c** ICU LOS d: ARDS). For graphic representation of all outcomes explored, please refer to the supplemental digital content. Brackets over bars represent adjusted Odds Ratios or beta-coefficients for the same outcomes. Groups: 1: <250 mL of platelet transfusion; 2: 250–300 mL; 3: 301–540 mL; 4: >540 mL

non-massively transfused patients sustaining severe blunt trauma. This effect does not appear to be linear, as the third quartile of PLT volume only increased the risk by a factor of approximately 1.4, and this did not reach statistical significance. All linear and logistic regression models demonstrated satisfactory goodness-of-fit and areas under the curve

Table 4 Adjusted Odds Ratios/beta-coefficients for clinically relevant outcomes, controlling for age, pre-hospital Glasgow Coma Scale, Injury Severity and APACHE II scores, comorbidities, crystalloid, colloid and blood product administration over the same time frame

	< 250 mL	≥ 250 mL	
			p
Mortality	Reference	1.24 (0.53 to 2.89)	0.620
ICU LOS	Reference	− 0.29 (− 2.39 to 1.80)	0.784
Hospital LOS	Reference	0.41 (− 3.53 to 4.37)	0.836
Ventilator days	Reference	0.44 (− 1.35 to 2.23)	0.629
ARDS	Reference	1.91 (1.10 to 3.33)	**0.022**
MOF	Reference	1.06 (0.64 to 1.75)	0.830
VAP	Reference	1.17 (0.71 to 1.92)	0.527
BSI	Reference	0.49 (0.26 to 1.01)	0.052
SSI	Reference	1.30 (0.66 to 2.56)	0.440
Non-infectious complications	Reference	1.31 (0.83 to 2.07)	0.239
Nosocomial infections	Reference	1.21 (0.77 to 1.92)	0.403

O.R. odds ratios; *95% CI* 95% confidence intervals; *ICU LOS* Intensive care unit length of stay; *ARDS* acute lung injury and acute respiratory distress syndrome; *VAP* ventilator-associated pneumonia; *MOF* multiple organ failure; *BSI* bloodstream infection; *SSI* surgical site infection

and C statistics for all models fitted ranged between 0.682 and 0.81. Polynomial and interaction terms were excluded as they were not found to be statistically significant and did not improve model fit.

Discussion

Great advances in the resuscitative management of the injured patient, with the widespread implementation of massive transfusion protocols across trauma centers worldwide, have resulted in notable survival improvements over the last few decades. However, no reliable predictors identifying what patients will end up requiring massive transfusion exist to date, and an ideal resuscitation strategy that can be employed with optimal outcomes in the NMT injured patient remains elusive. Recently, the use of FFP in non-massively transfused, non-coagulopathic injury victims has come under fire, with evidence demonstrating higher inflammatory and infectious complication rates [14, 20], and the pre-emptive use of blood products in patients without an obvious indication (coagulopathy for FFP; thrombocytopenia or platelet dysfunction for PLT transfusion) and no anticipated survival benefit (as is the case for massively transfused subjects) is anything but harmless. Complications of blood product transfusion are protein and include, but are not limited to, immune-mediated reactions that may range in severity from minor febrile reactions (approximately 1%) [21] to life-threatening anaphylactic attacks (1 in 20,000 transfusions) and hemolysis (1 in 6,000 transfusions) [7, 22]. Viral and bacterial infections, although rare, are still possible, despite strict screening protocols, and PRBC are known to confer a mild immune-compromising effect [22]. Platelet products carry the highest risk of contamination and thus resultant bacterial infection, due to their non-refrigerated maintenance [7]. Blood products have been further implicated with longer ventilation and ICU stays, likely due to the occasionally overzealous intravascular volume expansion they bestow [11] and their potential for triggering ARDS [23].

In our study, we identified that PLT is an independent predictor of ARDS development in non-massively transfused bluntly injured patients, and the risk appears to approximately double if patients receive more than 250 mL, or approximately 1 unit of PLT, even though the increase is not linear. This non-linear association may be attributed to the fairly low number of incidents recorded for each outcome per group (slightly over 100 patients per analyzed group with only a small fraction developing these complications), as evidenced by non-linear trends, specifically in the third quartile, seen also in other outcomes of interest (ICU LOS, ventilator days, MOS, and non-infectious complications) (Table 3). The fact that the higher incidence of ARDS does not lead to excess mortality is consistent with our previously published data [24]. TRALI is a term originally used by Popovsky et al. to describe non-cardiogenic acute pulmonary edema leading to respiratory failure complicating transfusion [25]. While TRALI has most commonly been associated with FFP transfusion [13], all blood components have been described to cause the syndrome with varying incidence [23]. Two mechanisms have been postulated to play a role in the pathogenesis of TRALI: The first is immune-mediated and involves the interaction between donor HLA antibodies and recipient HLA antigens. This antibody–antigen interaction activates leukocytes that can damage pulmonary epithelium and leads to ALI. The presence of mitochondrial DNA damage-associated molecular patterns (DAMPs) may also play a role in exacerbating this immune response [26]. Alternatively, lysophosphatidylcholine molecules from fatty acid breakdown that can accumulate in stored blood have the ability to prime lung-recruited neutrophils that can also damage pulmonary epithelium, if an inflammatory insult (such as severe trauma) already exists, with a mechanism that does not involve the innate immune response. Both proposed pathways converge to capillary rupture, fluid and protein exudation into the alveoli, leading to pulmonary edema and hypoxia [27].

The notion that platelets merely facilitate hemostasis is outdated, as they have been shown to be potent drivers of an inflammatory response, by expressing adhesion molecules that amplify pro-inflammatory cytokine production and

mediate neutrophil- and endothelial-induced tissue injury [28, 29]. Zarbock et al. demonstrated that platelet activation alone promotes neutrophil recruitment into the lungs [30], a factor we have shown to be necessary for ARDS development [31]. By reducing circulating platelets or by inhibiting platelet–neutrophil interaction through P-selectin inhibition, Zarbock and colleagues were able to stop progression of ARDS [30]. Similarly, Looney et al. demonstrated increased sequestration of platelets in the pulmonary parenchyma, associated with up to a 50% reduction in circulating platelet count, in a murine model of TRALI [32], and more recently higher levels of circulating pro-inflammatory cytokines and neutrophils in humans with TRALI [33]. These findings suggest that platelet–neutrophil interactions are a key step in the pathophysiology of ARDS, and our clinical data appear to endorse this proposed mechanism: It is known that circulating neutrophils become activated within 6–48 h after major torso injury [34], and this time corresponds roughly to the median time required for the syndrome to manifest clinically (approximately 2–3 days), allowing time for pulmonary neutrophil recruitment to peak and local tissue destruction to commence. Not surprisingly, PLT transfusions have been associated with longer ventilator and ICU stays, without improving mortality in NMT patients [11]. Additional support to our hypothesis that platelets play a key role in the pathogenesis of ARDS is provided by recent data that show that pre-hospital antiplatelet use is associated with lower incidence of ARDS [35, 36].

While PLT transfusions are known to confer a survival benefit in MT injury victims [37], a finding corroborated further with a recent prospective randomized clinical trial (PROPPR) [38], this effect does not appear to be maintained in trauma patients with less severe hemorrhage and who do not require massive transfusion [11]. PLT transfusion in NMT may in fact bestow preventable morbidity. Although there is a statistically significant trend on several other clinically relevant outcomes with transfusion of greater volume of platelets on univariate comparisons (Table 2), including duration of mechanical ventilation ($p = 0.001$); LOS in the ICU ($p = 0.001$) and the hospital ($p = 0.026$); incidence of MOF ($p = 0.001$) and non-infectious complications ($p = 0.017$), it appears that these outcomes may be related to the greater physiologic derangement (APACHE II $p = 0.018$), number of comorbidities (Charlson Comorbidity Index, $p = 0.011$), and volume of crystalloids ($p = 0.012$) and other blood products ($p < 0.001$) these patients received, as all these lose their statistical significance on multivariate regression (Table 3). One notable observation is that the incidence of bloodstream infections decreases by half [adjusted O.R. 0.49 (95% CI 0.26–1.01), $p = 0.052$] almost reaching statistical significance in the multivariate regression. It may be that the priming of the host neutrophils by PLT transfusions, as described earlier, may exert a protective effect against bloodstream infections, while being detrimental to normal lung function. One might also notice that the patients who received more PLT, also received more blood products and crystalloids. It is not possible to postulate what drove this decision-making, as slight variations exist in transfusion thresholds in the individual clinician and local institutional level. However, without reliable MT predictive methods, trauma providers may be aiming towards a 1:1:1 resuscitation and stop altogether when hemodynamics improve and hemostasis is achieved. Whether early PLT aided in achieving hemostasis, hence helping the patients not needing MT, is an interesting speculation that would have to be addressed with a prospective randomized study and intention-to-treat analysis that is beyond the scope of the current project.

Although we are the first to demonstrate an association between trauma-related PLT transfusion and ARDS, Nydam et al. reported a link between post-injury thrombocytopenia and multiple organ failure [39]. While in their article they propose numerous immune-mediated mechanisms, through which activated platelets may induce ALI, a key component of MOF [40], they did not include in their analysis the potential role of the transfused PLT, likely a key component in the pathogenesis of both highly lethal disease entities. A key difference, however, between our findings and those of the Nydam study is the lack of association between PLT transfusion and MOF development. The latter, though, did not adjust for crystalloid volume resuscitation, a factor increasingly identified to be associated with MOF [17, 18] and which could have additionally contributed to dilutional thrombocytopenia.

While the strengths of our analysis lay in our robust data source (a multi-institutional, prospectively collected and well-validated database) and our ability to control for numerous confounders, various limitations have to be kept in mind: The retrospective nature of our review, and the fact that the database did not specifically address allergic transfusion-related complications. More importantly, the precise indication for PLT transfusion is not clearly defined, as it cannot always be inferred whether they were administered prophylactically in the setting of anticipated MT (which was stopped early due to prompt bleeding control), or to treat perceived functional (as in pre-existing antiplatelet use) or absolute thrombocytopenia. Platelet counts before and after transfusion were also not available, a factor which limits our understanding of the non-linear association of PLT product administration and ALI/ARDS incidence. Additionally, we were unable to look at specific ratios between blood products within short time intervals, as the data were not collected within narrow time frames.

Patients sustaining greater blood loss are likely to require larger blood product volumes and experience poorer outcomes, likely as a result of the resuscitation

or as a direct consequence of the systemic inflammatory response commonly seen after severe trauma or large volume component transfusion [41]. In our analysis, we adjusted for injury burden, acute physiologic derangement, age, and also fluid and blood product resuscitation—all factors known to be associated with adverse outcomes after trauma. Not surprisingly, subjects receiving greater volumes of PLT also received higher volumes of crystalloids and total blood products. This fact translated to a higher incidence of ARDS and MOF, and thus longer ventilation, ICU and overall hospital stays, but not increased mortality. This is consistent with our previously published results, further corroborating that ARDS may not be as deleterious in trauma patients, as is in other critically ill patients [24]. After adjusting, however, for other resuscitation and transfusion, PLT administration alone was found to be an independent risk factor for ARDS development in a non-linear fashion, likely for the reasons delineated earlier.

The retrospective nature of this analysis precludes issuing a strong recommendation on the use of PLT transfusion in the severely injured patient. However, the astute trauma clinician aiming at minimizing pulmonary morbidity from PLT transfusions should consider increasing the threshold for initiating PLT therapy only in the presence of true or functional thrombocytopenia; when the PRBC and FFP transfusions approach MT thresholds and achieving hemostasis is anticipated to be more than 1–2 h away; and/or stopping their administration as soon as it becomes clear that MT will not be required; screening donors for leukocyte antibodies, including Human Neutrophil Antibodies (HNA-1a, HNA-1b, HNA-2 and HNA-3a) and HLA class I and II [42]; and minimizing to the extent possible transfusing PLT originating from donors at risk for leukocyte antibody formation, namely parous women and previously transfused or transplanted subjects [43].

Conclusions

PLT transfusion in NMT blunt trauma patients independently increases risk for ARDS and should be avoided in the absence of true or functional thrombocytopenia, provided that the estimated risk for death from exsanguination is acceptably low, and once the need for MT has been ruled out.

Author contributions GK and NS were responsible for the study design, statistical analysis and manuscript drafting; EN for database maintenance and statistical analysis; BS, PB and RT for critical manuscript revision; and PB, DR and RT for providing overall oversight and critical manuscript revision; RT is the main PI for the Glue Grant project.

Funding The Glue Grant was a NIH-NIGMS supported collaborative. No funding was obtained for this secondary analysis.

Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest, and all human studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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