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Anti-Platelet Therapy is Associated With Decreased Transfusion-Associated Risk of Lung Dysfunction, Multiple Organ Failure, and Mortality in Trauma Patients

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Abstract

Objective—To determine whether pre-hospital anti-platelet therapy (APT) was associated with reduced incidence of acute lung dysfunction, multiple organ failure (MOF), and mortality in blunt trauma patients.

Design—Secondary analysis of a cohort enrolled in the NIGMS Trauma Glue Grant database.

Setting—Multicenter study including 9 US level-1 trauma centers.

Patients—A total of 839 severely injured blunt trauma patients at risk for MOF (age >45 years, base deficit > 6 mEq/L or systolic blood pressure < 90 mmHg, who received a blood transfusion). Severe/isolated head injuries were excluded.

Measurements and Main Results—Primary outcomes were lung dysfunction (defined as grades 2–3 by the Denver MOF score), MOF (Denver MOF score >3), and mortality. Patients were documented as on APT if taking acetylsalicylic acid, clopidogrel, and/or ticlopidine. Fifteen percent were taking APT prior to injury. Median injury severity score (ISS) was 30 (interquartile range, IQR: 22–51), mean age 61 ± 0.4 years and median red blood cells (RBC) volume transfused was 1700 ml (IQR: 800–3150ml). Overall, 63% developed lung dysfunction, 19% had MOF, and 21% died. After adjustment for age, gender, comorbidities, blood products, crystalloid/12hrs,

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presence of any head injury, ISS, and 12hrs base deficit >8 mEq/L, 12 hrs RBC transfusion was associated with a significantly smaller risk of lung dysfunction and MOF among the group receiving APT compared to those not receiving it (lung dysfunction $p=0.0116$, MOF $p=0.0291$). In addition, APT had a smaller risk (albeit not significant, $p=0.06$) of death for patients receiving RBC compared to those not on APT after adjustment for confounders,

Conclusions—Pre-injury APT therapy is associated with a decreased risk of lung dysfunction, MOF, and possibly mortality in high-risk blunt trauma patients who received blood transfusions. These findings suggest platelets have a role in organ dysfunction development and have potential therapeutic implications.

Keywords

Antiplatelet Agents; Trauma; Multiple Organ Failure; Lung Dysfunction; Blood Transfusion

INTRODUCTION

Lung dysfunction remains a leading cause of morbidity and mortality among critically ill patients (1). Ultimately, progression to acute respiratory distress syndrome and multiple organ failure (MOF) may ensue, further worsening outcomes. In spite of extensive research into the mechanism, effective pharmacologic treatments and preventative agents have yet to be discovered. Over the past decade, only low-tidal volume ventilation has been shown to improve outcomes from ventilator-associated lung injury and lung dysfunction. However, severely injured trauma patients are a unique population who have an unusually high incidence of lung dysfunction (70%) (2). Since the care of trauma patients is usually complicated by hemorrhage and coagulopathies, this population is more likely to receive blood products, a known independent risk factor for post-injury pulmonary dysfunction and MOF (3–6).

A maladaptive inflammatory response has been implicated in the pathogenesis of lung dysfunction and MOF (7–9), and emerging research is showing a highly conserved coupling of both the coagulation and immune systems in inflammatory states (10). Recent studies have implicated platelets as one of the prominent cellular mediators in sepsis, transfusion, and trauma related organ failure, which when inhibited, attenuates the associated neutrophil-mediated injury (11–13). Therefore, we hypothesized that pre-hospital anti-platelet therapy (APT) would be associated with a decreased incidence of transfusion-associated lung dysfunction, MOF, and mortality in a high-risk trauma population.

MATERIALS AND METHODS

Between 2001 and 2008, high-risk trauma patients from nine trauma centers were prospectively enrolled in the multi-institutional Inflammation and Host Response to Injury (Glue Grant) study, approved by the institutional review board at each participating institution (14). Inclusion criteria for the Glue Grant study included: blunt trauma mechanism, emergency department (ED) arrival within 6 hours of injury, ED base deficit 6 mEq/L or ED systolic blood pressure < 90 mmHg, and a blood product transfusion within the first 12 hours of ED arrival. Exclusion criteria were: anticipated survival of < 24 hours, pre-existing medical conditions with expected survival < 28 days, severe traumatic brain injury (defined as a GCS ≤ 8 after ICU admission AND brain computerized tomography scan abnormality within first 12 hours after injury) with no other body region injury, and pre-existing immunosuppression/organ dysfunction. For more details on entry/exclusion criteria please visit the Glue Grant website: <http://www.gluegrant.org>. In addition, we limited this analysis to individuals older than 45 years of age, based on our previous study

showing that the increase in post-injury adverse outcomes starts at this age threshold. (15). This is also the age group for whom APT is much more prevalent (15% compared to only 1% of the patients younger than 45 years). Patients were followed for 28 days.

Patients on APT included those who had documentation of currently taking acetylsalicylic acid (ASA) or a specific "other anti-platelet" agent (including clopidogrel or ticlopidine) in the Glue Grant database.

The primary end-points were: 1) lung dysfunction, defined as a Denver lung dysfunction score grades 2 or 3, which corresponds to $\text{PaO}_2\text{:FiO}_2$ ratio < 200 (16), 2) MOF (Denver MOF score > 3) (17), and mortality. Crude associations were assessed by the Chi-square test for categorical variables and by the t-test or the Wilcoxon non-parametric test for continuous variables. Using a logistic regression model, the independent association between pre-injury APT and the outcomes was adjusted for known risk factors of post-injury organ dysfunction and mortality: 1) demographic characteristics (age, gender, comorbidities), 2) anatomic injury severity (injury severity score (ISS), a validated score that measures the severity of the anatomic traumatic injury and presence of mild/moderate head injury), and 3) shock severity (volume of blood product transfusions in the first 12 hrs, base deficit in the first 12 hrs, and crystalloid volume in the first 12 hrs). It should be noted that the Glue Grant definition of comorbidities is quite broad, resulting in a large proportion of patients with pre-injury conditions. All pertinent interactions between the independent variables were tested by including interaction terms and testing for significance in the logistic regression model. A p-value < 0.05 was considered significant.

RESULTS

Overall, 839 patients were eligible for the analysis, of whom 128 (15.3%) had documented pre-injury APT use. Specifically, 66% of the 128 patients on APT were receiving ASA, 20% received "other antiplatelet agents" and 14% received "ASA plus another antiplatelet agent". There were no significant differences between patients taking ASA and those taking "other antiplatelet agents", regarding age, gender, injury severity or outcomes. Table 1 depicts the characteristics of the study population and the incidence of adverse outcomes, stratified by pre-injury APT status. As expected, APT patients were older, and had significantly more comorbidities than non-APT patients. They were also more severely injured but received a similar volume of blood products; however, APT patients were less likely to receive a massive transfusion (> 10 Units PRBCs/12 hours) compared to non-APT patients (17.2% vs. 27.7%; $p=0.01$). We did not detect significant differences in the crude rates of lung dysfunction, MOF, and death, as well as ICU stay and mechanical ventilation time.

After adjustment for possible confounders (age, gender, comorbidities, ISS, presence of mild/moderate head injury, base deficit > 8 mEq/L in the first 12 hrs, crystalloids and volume of PRBC, FFP and platelets transfused in the first 12 hrs), we identified a significant interaction between blood transfusions and APT. Specifically, transfused patients on APT had significantly lower odds ratios (OR) of lung dysfunction and MOF compared to transfused patients who were not on APT at time of injury (interaction PRBC $\times$ APT $p=0.0116$ for lung dysfunction, $p=0.0291$ for MOF). Figures 1 and 2 illustrate the adjusted odds ratios for lung dysfunction and MOF by volume of PRBC transfused within 12 hours post-injury stratified by APT status.

Transfused patients on APT had lower mortality adjusted OR compared to patients who were not on APT, albeit not significantly (interaction PRBC $\times$ APT $p=0.0633$) as shown in Figure 3.

Interactions between other blood products (platelets, FFP) transfused within 12 hours and APT were not significant for any of the tested outcomes (interaction p values all between 0.19 and 0.97). We repeated these multivariate analyses after excluding patients with mild/moderate head injuries (as opposed to controlling for its presence as in the above described models), and the results remained essentially the same.

DISCUSSION

Among transfused patients, platelet inhibition therapy had a significant negative association with lung dysfunction and MOF in trauma patients, and appeared to be related to a decrease in mortality, in agreement with pre-clinical basic science experiments and other clinical studies, implicating platelets in multiple organ dysfunction. Lung dysfunction and MOF continue to have a high incidence in critically ill patients, increasing the amount of hospital care, length of stay, and healthcare costs, not only in the short-term, but years following the injury (18). Their high morbidity, mortality and high resource utilization underscore the importance of preventing these lethal syndromes.

The pathogenesis of postinjury organ dysfunction has not been fully elucidated, but involves extensive interactions between both coagulation factors and inflammatory mediators irrespective of the etiology. These interactions ultimately result in increased pulmonary fibrin deposition and microthrombi formation (16,19). However, clinical studies specifically employing anticoagulation and fibrinolytic therapies to prevent fibrin deposition and microthrombi have failed to show improved outcomes (25). A recent example is the use of activated Protein C in critically ill patients. The protective effects of activated Protein C is believed, in part, to be due to the proteolytic cleavage of factors Va and VIIIa, and the inhibition of plasminogen activator-inhibitor 1 (PAI-1) resulting in increased anticoagulation and improvement in tissue microcirculation. Apart from this proposed mechanism, the PROWESS-SHOCK study failed to show a survival benefit (26).

Platelets possess hemostatic and thrombotic elements, but also have known inflammatory properties, which could propagate lung injury (27,28). Platelet activation, which likely promotes a complex interaction between the pulmonary endothelium and neutrophils, can occur via multiple platelet agonist/receptor interactions in the setting of trauma, transfusion, or sepsis; collagen (GP IV), thrombin (PAR1 and PAR4), ADP (P2Y₁ and P2Y₁₂), thromboxane A₂ (TP), and epinephrine (α_{2A}) (29). Growing evidence is showing that the platelet-endothelium interaction mediated through platelet P-selectin is vital in the pathogenesis of acute lung injury through the recruitment of neutrophils (12,30).

Platelets have been indirectly implicated in lung injury since the early 1980's with studies involving platelet activating factor (PAF) (31). PAF is a phospholipid derivative released from stimulated macrophages, basophils, and platelets, and is an effective activator of both neutrophils and platelets. This study revealed that intravenous administration of PAF induced both hypotension and bronchoconstriction, which was also accompanied by thrombocytopenia. They further concluded that PAF-mediated bronchoconstriction was decreased with aspirin use, as well as platelet depletion, further supporting the role of platelets in lung injury. Interestingly, prior work from our lab has shown that early refractory thrombocytopenia is a predictor of ALI/ARDS, MOF, and mortality suggesting platelet activation and sequestration as a mechanism (32). Yet, there appears to be no association with platelet transfusion and worse outcomes following trauma, as opposed to fresh frozen plasma and PRBC (33).

Since the implication of platelets in lung injury models, there has been some supporting evidence of an association between APT and reduced rates of adverse outcomes in critically

ill patients (34), while others have not been able to detect a difference (35,36). Our study focused specifically on a population of severely injured trauma patients, and supports an association between transfused patients using APT and reduced adverse outcomes.

In this specific high-risk trauma population, initiating therapies that could potentiate bleeding is of concern, but there is a paucity of literature evaluating outcomes in trauma patients taking APT. This study has shown that at low transfusion levels, APT users were, as expected, at higher risk for adverse outcomes than those not receiving APT. However, one must consider that APT patients may have had some increased bleeding compared to non-APT patients since they received a similar volume of blood products than non-APT patients, but had a lower ISS and lower base deficit in the first 12 hours. Alternatively, APT patients were less likely to receive a massive transfusion (> 10 units PRBCs) compared to non-APT patients. It is thus conceivable that the APT patients' less severe injury led to a lesser systemic inflammatory response, making the host less vulnerable to the harmful effect of blood product transfusions. Regardless, APT appeared to offer protection against one of the most important risk factors for organ dysfunction in trauma populations (blood transfusions) (5), and decreased the risk of lung dysfunction/MOF in patients with significant risk factors (increased age and comorbidities) (37,38).

There are several limitations to this study, including that the Glue Grant database assesses a specific group of severely injured patients, and thus, it is not possible to generalize these results to less seriously ill patients. In addition, APT agents have different mechanisms of action, and we were unable to conduct a sub-group analysis to determine the role of individual APT agents or combination therapy. We did not observe significant differences between patients taking ASA and those taking "other antiplatelet agents", regarding the endpoints studied; although the sample for these comparisons was small. Furthermore, the dose of APT and the reinstitution of APT could not be determined from the database, thus, we were unable to assess dose-dependent patterns and timing effects.

Retrospective studies always carry the possibility that results were due to chance; thus we used appropriate two-tailed statistical testing of pre-formulated hypotheses and pre-defined confidence level (95%) to minimize it. The hypotheses to be tested were motivated by findings from pre-clinical animal experiments demonstrating that changes in platelet function affected outcomes. In a reverse translational approach, we tested our pre-clinical research findings in the clinical arena using a large multi-institutional study set up to find risk factors for postinjury adverse outcomes.

In spite of these limitations, there seems to be clear associations with APT and decreased transfusion-associated organ dysfunction and mortality. Since increased age and comorbidities are significant risk factors for organ dysfunction and mortality in trauma, patients on APT should have had worse outcomes (37,38). However, these patients had similar endpoints regarding lung dysfunction, MOF, and mortality in our univariate analysis compared to those much younger and with fewer comorbidities. Moreover, after adjustment for these confounders, APT was found to be associated with decreased lung dysfunction, MOF, and mortality in patients receiving PRBC transfusion, which is a significant risk factor for these outcomes. Our findings provide support for future studies aiming to assess the effects of anti-platelet therapy.

CONCLUSION

Severely injured, high-risk trauma patients taking anti-platelet therapy prior to injury have a decreased risk of lung dysfunction, MOF, and mortality. These results continue to support pre-clinical studies demonstrating improved outcomes with APT following trauma and

hemorrhagic shock. Multiple platelet antagonists are commercially available, inexpensive, and have known risk profiles. Collectively, the growing evidence implicating platelets in the pathogenesis of lung dysfunction and MOF, and these observational studies demonstrating a role of APT in preventing these conditions, justifies further examination of specific APT agents in treating, or even preventing, adverse outcomes in critically ill patients.

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Figure 1.

Adjusted odds ratios of lung dysfunction (measured by the Denver MOF score grade 2 or 3) among patients on anti-platelet therapy (APT) compared to those not on APT by units of packed red blood cells (PRBC) received in the first 12 hours post-injury (also adjusted for age, gender, comorbidities, ISS, head injury, and base deficit >8 mEq/L, crystalloids and blood products in the first 12 hrs). APT patients receiving 6 RBC units in the first 12 hours were 0.9 less likely to develop lung dysfunction, or non-APT patients were 1.14 more likely to develop lung dysfunction than patients on APT. The adjusted odds ratios further decreased with the number of RBC units transfused.

Figure 2.

Adjusted odds ratios of MOF (measured by the Denver MOF score >3) among patients on anti-platelet therapy (APT) compared to those not on APT by units of packed red blood cells (PRBC) received in the first 12 hours post-injury (also adjusted for age, gender, comorbidities, ISS, head injury, and base deficit >8 mEq/L, crystalloids and blood products in the first 12 hrs). APT patients receiving 6 RBC units in the first 12 hours were 0.8 less likely to develop MOF, or non-APT patients were 1.25 more likely to develop MOF than patients on APT. The adjusted odds ratios further decreased with the number of RBC units transfused.

Figure 3.

Adjusted odds ratios of mortality among patients on anti-platelet therapy (APT) compared to those not on APT by units of packed red blood cells (PRBC) received in the first 12 hours post-injury (also adjusted for age, gender, comorbidities, ISS, head injury, and base deficit >8 mEq/L, crystalloids and blood products in the first 12 hrs). APT patients receiving 6 RBC units in the first 12 hours were 0.8 less likely to die, or non-APT patients were 1.25 more likely to die than patients on APT. The adjusted odds ratios further decreased with the number of RBC units transfused.

Table 1

Population characteristics

	Receiving Pre-APT		P-value
Demographic	Yes (N=128, 15%)	No (N=711, 85%)	
Age (years), Mean (SEM)	69 (1.0)	59 (0.4)	<0.0001
Male gender, N (%)	93(73%)	441 (62%)	0.02
Comorbid, N (%)	126 (98%)	583 (82%)	<0.0001
Injury Severity			
Injury severity score, Median (IQR)	29 (20–36)	33 (22–41)	0.004 *
RBC/12hrs (ml), Median (IQR)	1600 (900–2450)	1750 (800–3300)	0.47 *
FFP/12hrs (ml), Median (IQR)	375 (0–1378)	550 (0–1471)	0.21 *
Platelet/12 hrs (ml), Median (IQR)	0 (0–300)	0 (0–267)	0.14
Base Deficit first 12 hrs Mean (SEM)	9.1 (0.4)	10.6 (0.2)	0.005
Mild/mod head injury, N (%) $\square$	22 (17%)	172 (24%)	0.08 ^
Crystalloids/12hrs (ml), Median (IQR)	7472 (5118–11344)	9500 (6775–13120)	<0.0001 *
Outcomes			
Lung Dysfunction, N (%) **	70 (58%)	415 (64%)	0.23 ^
MOF, N (%) ***	20 (17%)	131 (21%)	0.37 ^
Death, N (%)	25 (20%)	149 (21%)	0.71 ^
ICU days, Median (IQR)	12 (5–21)	11 (5–19)	0.29 *
Ventilation days, Median (IQR)	7 (2–16)	7 (3–15)	0.63 *

* Wilcoxon non-parametric test (all other p-values were from Chi-square tests for proportions or T-test for continuous variables unless otherwise indicated)

** 65 patients had missing data on PaO₂/FiO₂

*** 90 patients had missing data to calculate MOF score

□ Patients with severe head injuries were excluded, these are mild or moderate head injuries

^ Chi-square Test

RBC: red blood cells

FFP: fresh frozen plasma

GCS: Glasgow Coma Scale

MOF: multiple organ failure