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PULMONOLOGY IN COMBAT MEDICINE (G EAPEN, SECTION EDITOR)

Transfusions in trauma

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Abstract Trauma associated with massive bleeding carries a high mortality even in the setting of early care in a trauma center. Such patients develop a significant coagulopathy soon after injury which contributes to these poor outcomes. Practices such as aggressive resuscitation with crystalloid fluids and red blood cell (RBC) transfusions appear to be associated with worse outcomes when compared to a practice of early blood product resuscitation with a ratio of plasma to platelets to RBCs approaching 1:1:1. Early therapy with tranexamic acid (TXA) appears beneficial as well, perhaps helping to prevent fibrinolysis. Viscoelastic testing offers advantages over conventional coagulation testing in the evaluation of further fibrinolysis and offers some guidance for additional targeted therapy. Many societies and organizations have released updated guidelines and recommendations that reflect these changes.

Keywords Trauma · Transfusion · Resuscitation · Coagulopathy

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Introduction

The approach to resuscitation and transfusion strategies for trauma patients suffering from life-threatening hemorrhage has undergone significant change over the last 15 years. In civilian trauma centers, less than 3 % of trauma patients experience massive bleeding that would prompt a need for a massive transfusion of blood products (this term is variably defined but most often describes those patients who require at least 10 units of RBCs within 24 h) [1]. The experience and data from military medical care provided to patients with combat trauma in Iraq and Afghanistan prompted a more extensive reevaluation of previously held beliefs and practices, in particular those associated with patients requiring a massive transfusion of RBCs [2]. Following the experience of military medical care of trauma patients, new studies in the civilian trauma population have shown that an early approach of transfusing plasma, platelets, and RBCs in a "balanced" ratio that approximates whole blood reduces hemorrhagic death [3••, 4•]. In medical patients, blood product transfusion has been associated with harm to include acute lung injury, circulatory overload, and increased risks of infection [5, 6]. In patients with upper gastrointestinal bleeding, more aggressive transfusions of RBCs targeting a hemoglobin of at least 9 mg/dL were associated with decreased survival compared to a more restrictive transfusion strategy [7]. Therefore, it is important that intensivists understand the differences in safety and efficacy of blood product resuscitation in trauma as compared to the management of medical bleeding or the euvolemic critically ill patient. Additionally, intensivists should understand that advances in laboratory monitoring beyond usual coagulation testing may provide a more rapid assessment of the coagulopathy associated with trauma and allow for targeted interventions. Finally, all health-care systems that can anticipate the potential for providing care to trauma patients should

develop a plan to manage those in need of early, aggressive resuscitation with blood products.

Hemorrhagic death in trauma

Within the first several hours after traumatic injury, most deaths are due to exsanguination, while multisystem organ failure is the most common cause of late death due to trauma. In a review of US combat deaths from Iraq and Afghanistan, hemorrhage accounted for over 90 % of the deaths from potentially survivable injuries [8]. Field management of such injuries includes the use of tourniquets and hemostatic dressings [9•]. Early, abbreviated surgical control of bleeding, termed "damage control surgery," has been practiced for over 20 years and improves survival [10]. However, the optimal approach to the resuscitation before, during, and after damage control surgery has been unclear until more recent studies. In addition to the vascular disruption from the injury itself, the hemorrhage due to trauma is complicated by an associated coagulopathy. This acute coagulopathy of trauma arises from tissue injury, shock, acidemia, and hypothermia [11] and is measurable from the time of the injury itself [12]. It is often made worse due to dilution following resuscitation with crystalloids or blood products. The "deadly triad" of acidemia, coagulopathy, and hypothermia provides targets for resuscitative strategies designed to improve outcomes [2]. Effective resuscitation strategies must address both hemorrhagic shock and the acute coagulopathy of trauma while seeking to avoid longer-term complications of organ dysfunction associated with overuse of blood products.

Historical approach to transfusions in trauma

There has been a significant shift in the use of transfusions in the early treatment of trauma-related hemorrhage. From the early 1980s, patients with shock were often treated with therapy designed to target supraphysiologic values of cardiac output and oxygen delivery, with data suggesting this might improve outcomes [13]. Although the practice of aggressive fluid resuscitation was challenged specifically in the setting of penetrating trauma [14], Advanced Trauma Life Support (ATLS) guidelines from 2008 [15] continued to recommend normalization of blood pressure with crystalloid resuscitation followed by additional crystalloid boluses and transfusion of RBCs for persistent hypotension. Additional blood products such as plasma and platelets were recommended only in response to laboratory data demonstrating a coagulopathy. Studies suggested this approach may worsen the coagulopathy and increase tissue edema, potentially causing harm. A 2006 survey of trauma institutions found few institutions with well-defined protocols to address the preparation, process, and monitoring of a massive transfusion [16].

The experience of managing combat trauma in Southwest Asia contributed to the development of "damage control resuscitation," an approach centered on the early use of blood product resuscitation based on components in the ratio of whole blood or the transfusion of fresh whole blood itself [2]. This approach was described in a clinical practice guideline for the management of life-threatening hemorrhage in the setting of combat trauma [9•]. Retrospective studies of transfusions in combat trauma management suggested a significantly improved survival was associated with a higher ratio of plasma to RBC transfusion [17, 18]. Overall, survivability of battlefield injuries improved from 80 % in World War II to 84 % in Vietnam to 90 % in Operation Iraqi Freedom/Operation Enduring Freedom [8]. As is often the case, this recent combat care experience led to a reexamination of trauma practices in civilian facilities.

Resuscitation: current evidence and strategies

Transfusions and damage control resuscitation

In contrast to previously held beliefs, targeting hemodynamic and perfusion goals with crystalloid, synthetic colloids, or albumin has not shown improved outcomes in traumatic injury and may cause harm [14, 19, 20]. Hydroxyethyl starch solutions are not recommended for use in critically ill adults in the USA due to an association with adverse outcomes such as kidney injury [21]. Albumin has been associated with a higher mortality rate when used for resuscitation of patients with traumatic brain injury [22]. When crystalloids were used in a higher plasma to RBC ratio in patients requiring a massive transfusion, a larger crystalloid volume was associated with increased morbidities to include acute respiratory distress syndrome and acute renal failure [23]. It appears that such fluids are potentially harmful when used to restore intravascular volume in the setting of hemorrhage.

Consequently, more recent research in trauma transfusion has been on the component ratios of blood products and timing of their delivery. Since 2004, US military clinical practice guidelines recommended early resuscitation with either fresh whole blood or component therapy with a ratio of plasma to platelets to RBCs of 1:1:1 [9•]. Studies of both military and civilian trauma populations have sought to determine the impact of such therapy on survival. Challenges in such studies include managing the impact of survivor bias and determining the optimal ratio and timing of blood product components.

An early retrospective study of outcomes of 246 patients requiring a massive transfusion (10 units of RBCs in the first 24 h) at a US combat support hospital in Iraq demonstrated an association with improved survival among the patients receiving a higher ratio of plasma to RBC transfusions, primarily as a result of decreasing death due to hemorrhage [18]. A

retrospective study of a similar population of combat trauma patients who received any blood products (not necessarily a massive transfusion) showed plasma transfusion was associated with increased survival as compared to transfusion of RBCs [17]. However, several retrospective and prospective cohort studies in civilian trauma centers showed conflicting results in finding an association with survival for an increased ratio of plasma to RBC transfusions [24, 25–28]. The authors felt these results could be a result of survival bias, specifically the possibility that only those patients who survived long enough received a high plasma to RBC transfusion ratio.

The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) study was designed to address the potential impact of survivor bias on the question of optimal ratios of blood products in damage control resuscitation. This trial accounted and controlled for the timing of blood product transfusions across much shorter intervals than other trials. The study results suggested that higher plasma to RBC (at least 1:2) and platelet to RBC (at least 1:1) transfusion ratios were associated with decreased mortality at 6 h. Although the association with improved mortality did not persist beyond 6 h, most hemorrhagic deaths occurred within 3 h after arrival to the trauma center [4•].

Published in 2015, the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial was the first large, randomized multicenter trial of trauma resuscitation comparing targeted blood product ratios with enough power to assess survival as a primary outcome. The study enrolled 680 subjects based on meeting prediction criteria for the need for a massive transfusion, and randomized them to receive transfusions in a plasma to platelet to RBC ratio goal of 1:1:1 or 1:1:2 using a strict protocol of transfusions from containers of set ratios of blood products. The main outcomes were mortality at 24 h and 30 days. The differences between the 1:1:1 and 1:1:2 groups for mortality at 24 h (12.7 vs. 17.0 %) and 30 days (22.4 vs. 26.1 %) were not significantly different, and there were no differences between groups for any complication, such as sepsis, acute kidney injury, and ventilator days. However, the 1:1:1 group had a significantly shorter time to hemostasis and less early death due to exsanguination compared to the 1:1:2 group (9.2 vs. 14.6 %) [3••].

Given the results of these more recent studies, damage control resuscitation with a ratio closer to 1:1:1 appears to decrease early hemorrhagic mortality without leading to an increase in late mortality or complications as compared to a lower ratio of plasma and platelet to RBC transfusions. The safety findings are important as patients transfused with a 1:1:1 ratio will likely receive more plasma, the blood component most commonly associated with transfusion-related acute lung injury [5]. Despite this concern, rates of acute lung injury and acute respiratory distress syndrome showed no difference between the groups and were lower than those seen in similar study populations. It is thought that early use of blood product resuscitation limits the use of crystalloid, which may be more harmful to pulmonary vascular permeability than plasma [3••, 29].

Most deaths due to trauma occur soon after injury, and therefore, interventions designed to improve survival should be instituted as soon as possible. In fact, the median times for hemorrhagic deaths in the PROMMTT and PROPPR studies were 2.6 and 2.3 h [3••, 4•]. In the PROMMTT study, 67 % of the patients had not received plasma within the first 30 min of arrival to the trauma center, despite the presence of robust massive transfusion protocols [4•]. There is now a move to push this damage control resuscitation out to the field. In fact, prehospital transfusion of blood products in both military and civilian trauma populations has been associated with improved mortality in retrospective studies [30, 31]. Challenges include keeping sufficient plasma ready for transfusion without incurring waste. Ongoing studies include the use of modifications to ground ambulances to allow rapid thawing of plasma for use when indicated [32].

Although there remains disagreement on the precise ratio of blood products to transfuse in damage control resuscitation, clinical practice at some trauma centers and organizational guidelines have changed to reflect advances in the field (Table 1) [36].

Laboratory guidance of further transfusion

Despite the improvement in outcomes related to damage control resuscitation with balanced blood product transfusions, it is not clear that higher ratios of plasma to RBCs correct the coagulopathy of trauma [12, 37]. It is possible that additional benefit could be gained from targeted correction of coagulopathy measured rapidly at the bedside.

While the exact mechanism is unknown, the presence of shock appears to induce a relatively hyperfibrinolytic and anticoagulant effect on the clotting cascade. This is in part due to endothelial tissue plasminogen activator release in response to ischemia. The coagulopathy of trauma is compounded by hypothermia and acidemia. Hypothermia inhibits coagulation protease activity and inhibits platelet function. Acidemia reduces the activity of the factor Xa/Va complex by 50 % at a pH of 7.2 and 90 % at a pH of 6.8 [11].

The acute coagulopathy of trauma is associated with worse outcomes. Several studies have identified that a significant portion of trauma patients arrive coagulopathic. Conventional coagulation testing (CCT) includes prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen levels, and platelet counts. Advantages to these tests include standardized quality control and accepted normal values. However, these tests are static and do not individually or collectively give a comprehensive picture of the clotting cascade. Platelet counts do not assess platelet function. Bleeding time can assess platelet function but is not often used because it is impractical. PT

Table 1 Selected organizational guidelines on massive transfusion

US Army Institute of Surgical Research. Joint Theater Trauma System Clinical Practice Guideline (2013) [9•]	American College of Surgeons Trauma Quality Improvement Program (2013) [33]	Canadian National Advisory Committee on Blood and Blood Products (2011) [34]	European Task Force for Advanced Bleeding Care in Trauma (2013) [35]
1. Goal ratio of 1:1:1 for plasma, platelets, and RBCs 2. Consider cryoprecipitate with early transfusions 3. Use ROTEM to adjust transfusion support when available	1. Transfuse blood over crystalloid or colloid 2. Goal ratio of plasma to RBC between 1:1 and 1:2 3. Transfuse single-donor platelets for each six units RBCs transfused 4. Switch to goal-directed resuscitation when labs are available	1. Did not endorse a specific ratio 2. Stated a ratio of plasma to RBC of 1:2 would be a reasonable approach 3. Adjust transfusion support based on clinical course and laboratory results	1. Initial administration of plasma or fibrinogen 2. Ratio of plasma to RBC of at least 1:2 3. Maintain platelets above 100×10^9/L

and aPTT were developed to measure clotting factor deficiencies and have been adopted in other applications but do not accurately predict bleeding [38]. Another criticism of CCT is the time delay from sample to result. Consequently, there has been impetus to identify complementary testing which could rapidly and accurately reflect the entire clotting cascade in trauma patients.

Hartert first developed viscoelastic testing in 1948. This testing utilizes whole blood placed in a cup-like container with a cylindrical pin suspended from above so that the tip of the pin lies just above the base of the cup. The pin measures the sheer force as the blood is moved. That force is displayed numerically and graphically to represent clot formation and fibrinolysis. Two currently recognized methods of performing viscoelastic testing are thromboelastography (TEG) and rotational thromboelastometry (ROTEM). Though similar, these tests vary slightly in the method in which they move the blood. TEG is predominantly used in the USA. ROTEM is largely used in Europe and Canada [38]. Viscoelastic testing, unlike CCT, provides an early comprehensive picture of the clotting cascade [39].

To accelerate the clotting cascade, tissue factor can be added to blood used in viscoelastic testing. Rapid TEG (r-TEG) adds tissue factor to initiate the clotting cascade, and results can be available in 20 min [39]. Tissue factor-activated ROTEM is labeled EXTEM. The amplitude of the clot at 5 min after activation of the clotting cascade on EXTEM has been shown to predict the need for a massive transfusion [40].

Despite their similarities, TEG and ROTEM values are not interchangeable, and strict cutoff values associated with mortality are neither defined nor universally accepted. Nonetheless, there is a clear association between both the need for a massive transfusion and mortality with abnormal clot strength and hyperfibrinolysis on viscoelastic testing. In 2014, a conference of world leaders in trauma-induced coagulopathy and resuscitation determined that viscoelastic testing is the only test capable of identifying hyperfibrinolysis with specificity in a timely manner for trauma resuscitation [41•].

While there is promise in viscoelastic testing, concerns remain about the accuracy of the results. As of June 2015, there were only three studies that investigated the accuracy of TEG and ROTEM. Due to the paucity of available literature, the reviewers could not determine whether TEG and ROTEM were suitable tests for identifying trauma-induced coagulopathy in adult trauma patients who are bleeding. In addition, clot amplitude assessment intervals are not standardized across the literature; time to measurement has ranged from 5 to 15 min [38]. High fibrinogen can mask thrombocytopenia or impaired platelet function on viscoelastic testing. Therefore, no specific cutoff is recommended for platelet transfusion despite a correlation between platelet count and clot strength [41•].

Aside from availability, quality control is the major concern with viscoelastic testing. One study from the UK sent eight samples of blood to 18 TEG and 10 ROTEM labs. Samples included both normal and abnormal clotting parameters. The results were so varied that decisions to transfuse would have been different between the centers [41•].

Additional therapies

Tranexamic acid

Excess fibrinolysis appears to be a significant contributor to trauma-induced coagulopathy; hyperfibrinolysis is also associated with an increased mortality rate in bleeding trauma patients [41•]. Tranexamic acid (TXA) inhibits plasmin-facilitated fibrinolysis [42]. Published in 2010, the CRASH-2 trial evaluated TXA vs. placebo in over 20,000 trauma patients at 274 hospitals within 40 different countries. The patients who received TXA had a statistically significant reduction in overall mortality and bleeding. There was a lower incidence of vascular occlusion in the TXA group, though this was not statistically significant due to low numbers of that type of adverse event [43].

Since viscoelastic testing is specific for identifying fibrinolysis, it is recommended that this type of testing be used early in trauma resuscitation to identify patients with hyperfibrinolysis. However, if otherwise clinically indicated, testing results should not be used to withhold TXA. Furthermore, if viscoelastic testing is not available, TXA should be given empirically. The American College of Surgeons 2013 massive transfusion quality improvement guide supports the use of TXA either empirically within 3 h of trauma or in response to evidence of elevated fibrinolysis [33].

Trauma patients are initially coagulopathic, but later in their clinical course, they become hypercoagulable [11]. This may explain why TXA has not shown clinical benefit when administered later after trauma. An interesting signal from the CRASH-2 data showed that patients who received TXA greater than 3 h after their trauma actually had a higher odds ratio of death. Also, there was no difference in transfusion requirements or fibrinolytic assays between the treatment and placebo groups. This raises the question of an alternate pathway by which TXA affected mortality and transfusion requirements [44].

Recombinant activated factor VII

In theory, recombinant activated factor VII (rFVIIa) replaces endogenous factor VII that can be consumed when massive amounts of tissue factor are expressed in response to trauma. In addition, factor VII binds activated platelets to promote hemostasis. It is currently approved for the treatment of hemophilia.

Boffard et al. published their phase II trial in 2005, which demonstrated a significant reduction in transfusion of RBCs in severely bleeding trauma patients with the use of rFVIIa [45]. While this study showed promise, rFVIIa did not become standard therapy for bleeding trauma patients. In 2010, Levi et al. published an analysis of studies that used rFVIIa in an off-label manner. Their analysis of placebo-controlled trials included both trauma-related and non-traumatic usage of rFVIIa in 4468 patients. They determined that there was an increased rate of arterial, but not venous, thrombotic events associated with the use of rFVIIa. Arterial thrombotic events were also significantly associated with increased patient age. Among the trauma subset of trials (three total), there was not a statistically significant difference in arterial thrombotic events [46].

The phase III CONTROL trial evaluated the efficacy of rFVIIa in 573 trauma patients with refractory bleeding despite standard therapy. Their data demonstrated no difference in mortality, ventilator-free days, or renal replacement therapy. The patients treated with rFVIIa were noted to have lower transfusion requirements of RBC, plasma, and total transfusions but no difference in platelet, fibrinogen, or cryoprecipitate requirements. There was no significant difference between serious adverse events or thrombotic events between treatment and placebo groups. The study was underpowered, and therefore, conclusions regarding these endpoints should be taken in that context. The investigators mentioned in their discussion that as care improves in trauma, it becomes more difficult to determine if specific therapies impact mortality. The mortality rate in this study was half of the predicted mortality in the study design [47].

The American College of Surgeons currently does not recommend the routine use of rFVIIa in trauma [33]. After 10 years of studies and post hoc data collection, controversy remains regarding the appropriate use of rFVIIa in the trauma patient.

Prothrombin complex concentrate

Four-factor prothrombin complex concentrate (PCC) includes clotting factors II, V, VII, and IX. This in combination with fibrinogen concentrate may replace the necessary deficient clotting factors in trauma-induced coagulopathy. Factor VIII is rarely deficient as it is produced by the endothelium. Factor V is present in platelet granules [42]. PCC is currently approved for the reversal of coagulopathy associated with vitamin K antagonists (VKA). PCC has several advantages over plasma; it does not require refrigeration for storage and there are no concerns about ABO compatibility.

In 2012, Joseph et al. evaluated the response of trauma-induced coagulopathy to PCC. Their retrospective observational cohort analysis of trauma patients who received PCC at the discretion of the trauma surgeon found that PCC normalized INR in all the patients. Their analysis included both patients who received warfarin and those who had never been treated with that medication. The non-warfarin group of patients also had a significant reduction in PRBC transfusions after PCC administration [48]. There have been subsequent small studies showing promise for PCC as a standard therapy for bleeding trauma patients, but further studies are need to determine its role outside of VKA coagulopathy [49].

At the current time, there is also insufficient evidence to set a TEG or ROTEM trigger for PCC or plasma transfusion in trauma. Current guidelines recommend considering fibrinogen or cryoprecipitate when abnormalities in clot strength are detected on viscoelastic testing [41•]. Both the ACS and American College of Chest Physicians (ACCP) currently recommend PCC only for the reversal of warfarin-associated coagulopathy [33, 50].

Conclusion

Trauma patients who require a massive transfusion to treat life-threatening hemorrhage benefit from damage control resuscitation. Effective employment of this strategy of early

empiric transfusions with a balance of plasma, platelets, and RBCs requires advance preparation and coordination of care. Such an approach appears safe and effective in patients at high risk for hemorrhagic death. The use of rapid laboratory assessment of coagulation with viscoelastic testing provides an opportunity for additional targeted treatment of the acute coagulopathy of trauma. Early use of TXA is the only additional hemostatic therapy recommended at this time.

Compliance with ethical standards

Conflict of interest David Bell and Edward McCann declare that they have no conflict of interest.

Human and animal rights and informed consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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