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Authors:

Howard A. Werman, MD, FACEP, Professor of Emergency Medicine, Ohio State University, Columbus.

Robert Falcone, MD, FACS, Clinical Professor of Surgery, Ohio State University, Columbus.

Peer Reviewer:

Perry W. Stafford, MD, FACS, FAAP, FACCM, Professor of Surgery and Chief, Division of Pediatric Surgery, Robert Wood Johnson Medical School, New Brunswick, NJ.

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The Coagulopathy of Major Trauma and Massive Transfusion

The quiet of your slow night shift is suddenly broken when three young adults arrive by local ambulance. All three were unrestrained victims in a single-vehicle rollover. Amid the airways, lines, tubes, radiographs, and calls to the regional trauma center, you notice that blood continues to drip from orifices and open wounds. You have seen it before and you know it means something bad, but as you continue to handle the chaos and order more units of packed red blood cells, you ask if there is something you should be doing differently.

Introduction

Hemorrhage is the leading cause of preventable trauma death. In addition, the presence of acidosis, hypothermia, and coagulopathy not only contribute to ongoing blood loss, but also are early markers of poor prognosis in patients with hemorrhagic shock. However, the simple reversal of these individual events with restoration of intravascular volume using red blood cells and hemostatic factors may not always be effective. In fact, massive transfusion — defined as replacement of more than one blood volume in a 24-hour period — may have unintended consequences and complications. As with previous military conflicts, the current experiences in Iraq and Afghanistan have provided reasons to rethink blood component resuscitation.[1,2] In particular, the role of whole blood replacement and the development of peri-resuscitative coagulopathy have been explored.

This paper will review selected articles from the recent medical literature, asking questions that allow us to examine the role of blood component replacement, massive transfusion, and the development of early coagulation disorders in trauma victims and their survival. We will conclude with commentary on the just-published study of the role of antifibrinolytic therapy in reducing mortality after major trauma.

Why Does Injury Lead to Coagulopathy?

Source: Hess JR, Brohi K, Dutton RP, et al. The coagulopathy of trauma: A review of mechanisms. J Trauma 2008;65:748-754.

Most physicians simply attribute the development of coagulopathy to the dilutional effects of crystalloid resuscitation. Newer evidence suggests that the cause is multi-factorial.

The authors of this review article conducted a literature search using MEDLINE and PubMed. Their specific focus was on the role of the following areas in promoting coagulation defects in victims of trauma: tissue injury, shock, factor depletion, dilution, hypothermia, acidemia, and fibrinolysis. They identified 87 articles that specifically addressed this topic.

The articles reviewed suggest that coagulation disorders in trauma have a complex pathophysiology, including: activation or dysfunction of fibrin generation or both; platelet and endothelium dysfunction; relative inhibition of stable clot formation by anticoagulant and fibrinolytic pathways; and either

Executive Summary

- Coagulopathy after major trauma is multifactorial in origin and is most common in patients with head injury and long-bone fractures.
- Traditional transfusion triggers are consensus-based and not applicable to the multiple-trauma patient who is undergoing massive transfusion resuscitation.
- Hospitals are encouraged to develop a massive transfusion protocol that stresses the proactive use of FFP and platelets along with RBCs.
- An effective hemoglobin-based blood substitute is not likely to be available in the foreseeable future.

consumption or inhibition of coagulation proteases (dilution may play a role here). Inhibition of these proteases is common in hypothermic and acidotic patients.

Fluid shifts associated with blood loss, crystalloid infusion, and transfusion of packed red blood cells (PRBC) contribute to dilutional coagulopathy. Hypothermia and acidosis also contribute to coagulopathy and continued blood loss. Finally, there is a strong interaction between the coagulation system and inflammatory response.

The authors conclude that there are six main precipitants of coagulopathy in trauma: tissue trauma, shock, hemodilution, hypothermia, acidemia, and inflammation. Brain injury and long bone fractures are particularly prone to developing coagulopathy. Shock appears to be the most important factor in the development of early coagulopathy. This condition is found in 25% of severely injured patients and carries a four-fold increase in mortality.[3-5]

The mainstay of treating traumatic coagulopathy involves early damage-control surgery to stop the blood loss[6,7] combined with aggressive resuscitation of the patient. This latter approach will be discussed in the articles cited below. The authors noted that identifying the underlying factors leading to early coagulopathy can result in medical therapies directed at preventing this lethal complication, and they recommend that further studies are needed to better elucidate the underlying mechanisms, which lead to a dysfunctional coagulation system in victims of trauma.

Comment. This article is a short, comprehensive review of the mechanisms leading to early coagulopathy in the trauma patient, and a good primer on the subject. In addition to acidosis and hypothermia, which should be addressed by protecting the patient's thermoregulatory environment and the aggressive use of warmed fluid resuscitation, the role of PRBC transfusion is highlighted in this review. This article contains an excellent reference list for those interested in exploring this topic further.

In the Bleeding Patient, What Is the Current State of Blood Component Therapy?

Source: Practice guidelines for blood component therapy: A report by the American Society of Anesthesiologists Task Force on Blood Component Therapy. *Anesthesiology* ***1996;84(3):732-747.***

This article summarizes the deliberations of the Task Force on Blood Component Therapy established by the American Society of Anesthesiologists. The goal was to establish evidence-based recommendations for the transfusion of PRBC platelets, fresh frozen plasma (plasma), and cryoprecipitate. The task force reviewed some 140 articles that addressed the use of blood products in the peri-operative and peri-partum period and their impact on clinical outcomes.

The authors provide a good summary of the more common risks of blood component transfusion. They note a risk of non-hemolytic transfusion reactions between 1-5%. Hemolytic reactions are far rarer at 1:33,000; fatal hemolytic reactions occur at between 1:500,000 and 1:800,000. The authors note that transfusion-related hepatitis occurs in 0.03% per unit transfused, with hepatitis C causing 90% of post-transfusion hepatitis cases. Transfusion-acquired hepatitis B and HIV are extremely rare. Cytomegalovirus infection is the most common transfusion-related infection. An additional statistic cited in the study is the fact that in the United States transfused blood costs $5-7 billion annually. This is a conservative figure that does not include other blood components, administrative costs, and indirect costs from transfusion reactions.

Regarding peri-operative PRBC transfusion, the authors state that the major indications to transfuse are to 1) enhance oxygen-carrying capacity of blood and 2) replace volume. They cite studies that indicate young, healthy patients can lose 30-40% of blood volume, which may be successfully replaced with crystalloid. Studies evaluating the effects of anemia on outcome have yielded conflicting results. No trigger level for serum hemoglobin has been shown to be appropriate to initiate transfusion of PRBC, nor has a target to stop transfusions based on clinical outcomes been established.

Based on controlled and uncontrolled observational studies, the task force made the following recommendations (*see Table 1*):

• Transfusion is rarely indicated when the hemoglobin concentration is greater than 10 g/dL and is almost always indicated when it is less than 6 g/dL, especially when the anemia is acute.

Table 1: Consensus-based Transfusion Triggers

Product	
Packed RBCs	• Almost always indicated when hemoglobin < 6 g/dL • Clinical assessment of perfusion and oxygen delivery are used to determine if RBC transfusion is indicated with hemoglobin between 6 and 10 g/dL. • Rarely indicated when hemoglobin > 10 g/dL
Platelets	• Prophylactic platelet transfusion is generally ineffective. • Platelet transfusion rarely effective when thrombocytopenia is due to increased platelet destruction or consumption. • Trauma patients with microvascular bleeding usually require regular platelet transfusions when the platelet count is < 50,000/mm^3. • Assessment of risk for serious hemorrhage should be used to determine if platelet transfusion is indicated in trauma patients with microvascular bleeding when the platelet count is between 50,000 and 100,000/mm^3. • Trauma patients with microvascular bleeding rarely benefit from platelet transfusion when the platelet count is > 100,000/mm^3. • Platelet transfusion may be useful in patients with a known disorder of platelet function and microvascular bleeding, even if the platelet count is normal.
Fresh Frozen Plasma (FFP)	• Indicated for control of microvascular bleeding when the PT or aPTT is > 1.5 times control. • Indicated for control of microvascular bleeding in patients undergoing massive transfusion.
PT = prothrombin time; aPTT = activated partial thromboplastin time	

• The determination of whether intermediate hemoglobin concentrations (6-10 g/dL) justify or require RBC transfusion should be based on the patient's risk for complications of inadequate oxygenation.

• The use of a single hemoglobin "trigger" for all patients and other approaches that fail to consider all important physiologic and surgical factors affecting oxygenation are not recommended.

• When appropriate, preoperative autologous blood donation, intraoperative and postoperative blood recovery, acute normovolemic hemodilution, and measures to decrease blood loss (deliberate hypotension and pharmacologic agents) may be beneficial.

• The indications for transfusion of autologous RBCs may be more liberal than for allogeneic RBCs because of the lower (but still significant) risks associated with the former.

The authors further note that surgical patients suffer adverse outcomes from thrombocytopenia and that platelet transfusion can correct those deficits. With specific regard to platelet destruction, the task force made the following recommendations:

• Prophylactic platelet transfusion is ineffective and rarely indicated when thrombocytopenia is due to increased platelet destruction.

• Surgical and obstetric patients with microvascular bleeding usually require platelet transfusion if the platelet count is less than 50,000/mm^3 and rarely require therapy if it is greater than 100,000/mm^3. With intermediate platelet counts (50,000 to 100,000/mm^3), the determination should be based on the patient's risk for more significant bleeding.

• Platelet transfusion may be indicated despite an apparently adequate platelet count if there is known platelet dysfunction and microvascular bleeding.

Finally, the task force reviewed the relevant literature on fresh frozen plasma. The authors cite multiple studies demonstrating that significant coagulopathy does not occur until after transfusion of one blood volume or when there is a significant elevation of the PT or PTT more than 1.5 times normal values.[8-12]

The panel recommended the following guidelines for plasma transfusion:

• for correction of microvascular bleeding in the presence of elevated (> 1.5 times normal) PT or PTT;

• for correction of microvascular bleeding secondary to coagulation factor deficiency in patients transfused with more than one blood volume and when PT and PTT cannot be obtained in a timely fashion.

In 2006, an update was released by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies.

Source: Practice guidelines for perioperative blood transfusion and adjuvant therapies: An updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. By the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Anesthesiology 2006;105:198-208.

As expected, the emphasis of this article is with activity that occurs just before and during surgery. It stresses the importance of preoperative evaluation and preparation, monitoring for blood loss, and monitoring for inadequate perfusion and oxygenation of vital organs. Regarding the decision to transfuse red blood cells, the article states, "Despite a large volume of work that has been published since the last practice guidelines, the information needed to define precisely when a blood transfusion should be given is not available in the literature. Although multiple trials have evaluated transfusion thresholds on patient outcome, the literature is insufficient to define a transfusion trigger in surgical patients with substantial blood loss." In general, this update reaffirms the recommendations from the original article.

Comment. The original article and the update are well-reasoned reviews of the indications for the transfusion of PRBC, platelets, and fresh frozen plasma. These recommendations reflect the current U.S. practice of blood component transfusion, reflecting the conservative use of both platelets and fresh frozen plasma, typically in a reactive manner dictated by the patient's blood work and evolving condition. These recommendations are similar to other practice guidelines and reviews.[13-23] Obviously, the focus of the recommendations in these two reviews is transfusion in the peri-operative and perinatal period; however, many of the studies cited have been applied to trauma patients. This is a consensus document, and the recommendations are not based on double-blinded, controlled and randomized trials. However, up to now, these practices have dominated traditional resuscitation approaches in injury. The studies cited below are beginning to change this paradigm to a more proactive and empiric approach.

When Performing a Massive Transfusion, Does Changing the Ratio of Plasma, Platelets, and Blood Cells Improve Outcome?

Source: Holcomb JB, Wade CE, Michalek JE, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Ann Surg 2008;248:447-458.

The authors of this study note that massive hemorrhage is the leading cause of preventable post-traumatic death. These deaths occur in the first 2-6 hours post-injury and typically require massive transfusion of blood products. Traditional treatment consisting of crystalloid and packed red blood cell resuscitation with the subsequent use of plasma and platelets often leads to coagulopathy, acidosis, and hypothermia in massive transfusion. These authors questioned whether the more aggressive use of plasma and platelets might improve civilian trauma outcome.

They conducted a retrospective review of all trauma admissions to 16 Level I trauma centers. To be eligible for inclusion, patients must have received at least 10 units of PRBC with at least one unit of PRBC transfused in the emergency department. Patients who died within 30 minutes of arrival were excluded from the study. Demographic data, transfusion, laboratory studies, time of death after ED admission, and outcome data were recorded on all patients. Units of PRBC, platelets, and plasma were recorded at 6 and 24 hours. Plasma:PRBC and platelet:PRBC ratios were calculated according to methods used in previous studies. Outcomes were compared for low (< 1:2) and high (> 1:2) plasma:PRBC and platelet:PRBC ratios. The relationship between these ratios and survival was also analyzed.

A total of 1574 patients received at least one unit of PRBC; 467 received more than 10 units of blood. One patient died within 30 minutes of ED admission, leaving 466 patients for analysis. There were no significant differences in demographic data, Injury Severity Score (ISS), or regional abbreviated injury scores (AIS) among the groups. An FFP:PRBC and platelet:PRBC ratio of greater than 1:2 was associated with a statistically significant improvement in 30-day survival. Patients who had both high FFP:PRBC and platelet:PRBC ratios had the best 30-day survival (73%). The survival benefit was primarily sustained in patients with truncal trauma. There was no difference in death from multisystem organ failure, head injury, airway compromise, or other causes.

The authors conclude that by being more aggressive with both FFP and platelets, the mortality in civilian trauma requiring massive PRBC transfusion is improved. They note that this is similar to findings reported in the military trauma literature. The survival benefit is greatest in the reduction of early mortality from major truncal hemorrhage. They recommend a target goal of 1:1 for both FFP:PRBC and platelet:PRBC ratios in massive transfusion.

Comment. This retrospective study suggests that a more liberal use of platelets and plasma in the early resuscitation of truncal trauma is associated with improved survival. As with all retrospective studies, there is a high likelihood of selection bias. Additionally, the groups were not equally matched in the volume of crystalloid administered. As the authors note, there is some evidence that crystalloids have an independent pro-inflammatory effect.[24,25] Nonetheless, these findings are consistent with an emerging body of military and civilian experience

Table 2: Sample of a Massive Transfusion Protocol

Initial transfusion	• 10 units of type O packed RBCs (Rh-negative in females < 50 years old) • 6 units of type AB/Rh-negative FFP • 2 units of single-donor apheresis platelets
Subsequent transfusions	• 6 units of cross-matched or type-specific packed RBCs • 6 units of type-specific FFP • 1 unit of single-donor apheresis platelets

with aggressive plasma and platelet infusion. This study and others like it suggest that large, prospective studies of varying FFP:PRBC and platelet:PRBC ratios should be conducted.

Does the Timing of Plasma, Platelets, and Blood Cells Improve Outcome?

Source: Gunter OL, Au BK, Isbell JM, et al. Optimizing outcomes in damage control resuscitation: Identifying blood product ratios associated with improved survival. J Trauma 2008:65:527-34.

These authors point out that following airway control, identification and control of hemorrhage is a major determinant of outcome in major trauma. The authors note that coagulopathy is a major complication of early trauma, with 25% of patients presenting coagulopathic at initial resuscitation. Previous guidelines held that fresh frozen plasma should be administered when the patient's INR was 1.5 or greater. Unfortunately, they note a significant delay between obtaining the test result and actual transfusion due to prolonged laboratory turn-around and preparation of the plasma for infusion. The authors report their experience at an institution with a proactive trauma exsanguination protocol (TEP), which utilizes early infusions of plasma and platelets along with PRBC in major hemorrhage.

The study was conducted at a large academic Level I trauma center with more than 3600 admissions for traumatic injury. The institution convened a committee that reviewed their previous experience with massive transfusions along with protocols from other institutions and developed a trauma exsanguination protocol. Based on the clinical condition of the patient, the attending trauma physician activates the protocol, which includes 10 units of uncross-matched PRBC, 4 units of AB-negative plasma, and 2 units of platelets. Subsequent infusions include 4 units of PRBC, 4 units of plasma, and 2 units of platelets. The study compared patients who received blood according to the TEP to a cohort of patients who went directly from the trauma bay to the operating room and received greater than 10 units of PRBC. The groups were compared with respect to 30-day survival and unexpected survival (based on survival in a patient with < 50% TRISS probability of survival). Patients were also separated into patients with an FFP:PRBC ratio > 2:3 and platelets:PRBC < 1.5.

Two hundred fifty-nine (259) patients were included in the analysis, including 144 survivors. Nonsurvivors had higher ISS and TRISS scores, more penetrating trauma, and, as expected, a lower 24-hour survival rate. Patients with an FFP:PRBC ratio more than 2:3 or a platelet:PRBC ratio of 1.5 or more were more likely to survive, and logistical regression showed intraoperative plasma:PRBC ratio to be an independent predictor of mortality. When pre-TEP and TEP groups were compared, TEP patients had a statistically improved 30-day survival, a greater number of unexpected survivors, and fewer unexpected deaths than the pre-TEP group.

The authors conclude that a more proactive strategy of blood component resuscitation resulted in a better outcome in their trauma patients requiring massive blood transfusions. In a follow-up article, the authors note that the predefined transfusion protocol was associated with a reduced incidence of severe sepsis or septic shock (9% vs. 16%) and multiorgan failure (16% vs. 37%).[26] For those interested in developing such a protocol, the authors have written a description of that experience.[27]

Comment. This is a small retrospective evaluation of the effect of implementing a proactive massive transfusion protocol on patient outcome. (*See Table 2.*) The major criticism of this study is the circuitous manner in which the primary analysis was conducted, comparing survivors to non-survivors by combining the study groups. Additionally, the historical controls may not have matched the group of patients who were eligible for the TEP in many key respects. In addition, such a study cannot account for other changes in trauma care that may have contributed to better outcomes. The study question was more directly addressed in the second part of the analysis comparing the pre-TEP group to the TEP patients. Noting this limitation and the usual qualification regarding selection bias, this study again contributes to a building body of evidence that the early use of both plasma and platelets, especially in the early operative period, improves survival in trauma patients. Whether the effect is the result of a reduction in early coagulopathy or a reduction in the use of crystalloid infusion cannot be deduced from this study.

So, Did We Get It Wrong All These Years?

Source: Duchesne JC, Hunt JP, Wahl G, et al. Review of current blood transfusions strategies in a mature Level I trauma center: Were we wrong for the last 60 years? J Trauma 2008; 65:272-278.

As with the previous reports, these authors have drawn on the military experience where a ratio of plasma:PRBC of 1:1 has reportedly resulted in improved survival from major hemorrhage. They proposed to examine whether these results could be duplicated in the civilian environment.

The group conducted a 4-year retrospective review of all admissions to their large Level I trauma center. The main purpose of the study was to assess the impact of plasma:PRBC ratio in the first 24 hours of resuscitation on mortality, defined as discharge from the hospital. Exclusions included patients younger than 18 years, those who died in the emergency department, patients with non-survivable head injury, and those who did not receive any fresh frozen plasma. Patients were divided into those receiving less than 10 units of PRBC and those receiving 10 units or greater in the first 24 hours. Patients also dichotomized into those who received a 1:1 ratio (actually, patients who received one unit or more of FFP for every 2 units of blood) and a 1:4 ratio (those who received 2 or more units of PRBC for each unit of FFP).

Of the 2746 patients who were admitted during the study period, 626 (22.8%) received 10 units of PRBC or less in the first 24 hours, and 135 (4.9%) received more than 10 units. Of patients receiving 10 units of PRBC or less, 250 (40%) received FFP and 376 (60%) did not. When compared to patients receiving more than 10 units of PRBC, patients receiving 10 units or less had statistically lower ISS, lower mortality (16.8%), and greater systolic BP. For patients receiving 10 or less units of PRBC, there was a clinical (though not statistical) difference in mortality between plasma:PRBC ratios of 1:1 (11.8%) compared to 1:4 (21.2%) [$p = 0.06$].

When looking at the patients who received more than 10 units of PRBC, the groups were similar in terms of age, male gender, incidence of penetrating trauma, and ISS. However, there was a marked difference in mortality between plasma:PRBC ratios of 1:1 (26%) compared to 1:4 (87.5%) [$p < 0.0001$]. Logistical regression revealed that the plasma:PRBC ratio produced a statistically significant mortality risk of nearly 20-fold.

These authors conclude that in the patient requiring massive blood transfusion, plasma infusion producing a near 1:1 FFP:PRBC ratio has a significant impact on mortality. They note that these findings need to be confirmed in a prospective randomized trial.

Comment. The authors of this study point out in their introduction that the incidence of penetrating trauma after Hurricane Katrina rose from 30% to 57%; thus we know that the nature of the injuries changed during the study period. As with the other studies, one has to wonder if there are inherent differences not obvious in the statistical comparisons of gross demographics between the patients receiving plasma:PRBC ratios of near 1:1 versus those receiving 1:4 and whether those differences explained the difference in mortality. In addition, the effect of platelet transfusions is not addressed in this study.

Taken with the military experience and the evidence in the other retrospective reviews, this study supports the findings of recent retrospective studies suggesting that in patients requiring massive transfusion (standard definition seems to be greater than 10 units of PRBC), infusion of plasma and platelets represents a factor conferring improved survival. However, the key question is whether this is a cause-effect relationship or whether aggressive plasma and platelet infusions are simply a surrogate marker for an expected better prognosis. These authors were correct in suggesting that a prospective study is needed to confirm cause and effect.

Does the Need for Uncross-matched Blood Predict Massive Transfusion?

Source; Inaba K, Teixeira PGR, Shulman I, et al. The impact of uncross-matched blood transfusion on the need for massive transfusion and mortality: Analysis of 5,166 uncross-matched units. J Trauma 2008;65:1222-1226.

Blood component replacement therapy is an important factor in the management of major hemorrhage, the leading cause of preventable traumatic death. The authors of this study attempted to assess the impact of uncross-matched blood on trauma mortality and the need for further blood component therapy.

Patients admitted to a major trauma center over a 6-year period were retrospectively reviewed. Typically, 8 to 10 units of uncross-matched blood (UPRBC) were available for immediate use in major trauma. All charts were reviewed to determine the use of uncross-matched, type-specific, and fully cross-matched blood in addition to the use of plasma and platelets. Decisions regarding the transfusion of blood products were made at the discretion of the attending trauma surgeon. Each chart was abstracted for demographic information, ISS, GCS, as well as outcome measures such as ICU length of stay (LOS), hospital LOS, and mortality. Logistic regression was performed on all variables that were significantly different between patients receiving UPRBC and those not receiving these products to determine the impact of UPRBC on mortality. An analysis was also performed to determine predictors of massive transfusion, defined as receipt of 10 or more units of blood in the first 12 hours of admission.

During the study period, 4,241 (16.6% of total) patients received 29,345 units of PRBC. Of this

group, 1,236 (29.1%) received UPRBC. A total of 5,166 units of UPRBC were transfused. The following were noted in patients receiving UPRBC: The group was younger, male, and had a greater incidence of penetrating trauma and hypotension. They were also significantly more injured as measured by GCS, ISS, individual AIS scores, and initial hemoglobin values. This group also received significantly more PRBC (11.9 vs. 4.9 units), plasma (5.1 vs. 2.0 units), and platelets (1.1 vs. 0.4 units). The mortality for the patients receiving UPRBC was 39.6%, which was significantly higher than the 11.9% for those not receiving this blood component. Not surprisingly, mortality rose with a stepwise increase in the number of UPRBC transfused. A logistical regression including all of the significant factors affecting mortality still demonstrated that transfusion of UPRBC was an independent predictor of increased mortality (OR = 2.15, 95% CI 1.58-2.94). Bivariate analysis showed several independent predictors of massive transfusion: ISS > 20; AIS > 3 for head, abdomen, and extremity; penetrating trauma; and an initial systolic BP < 90 mmHg. A requirement for URBC was the most highly predictive of massive transfusion.

The authors conclude that based on their experience with patients requiring UPRBC, a significant amount of information can be garnered regarding these patients. In particular, these patients have a significant increase in expected mortality and are more likely to require massive transfusion therapy.

Comment. This study is somewhat intuitive in its findings. In this case, the obvious selection bias is actually the major study conclusion: The requirement for UPRBC obviously identifies a critically ill trauma patient by virtually every objective measure (injury scores, need for intubation, and outcome). These authors have done a solid job of quantifying the actual impact of UPRBC therapy on patient outcome. Equally important is the knowledge that receiving UPRBC can act as a trigger event for massive transfusion therapy and set in motion a more proactive approach to resuscitation for the patient requiring multiple units of blood. The independent predictive value of ED transfusion of UPRBC for early massive transfusion requirement was also identified in a smaller study of 485 patients.[28] Two scoring systems, the Trauma Associated Severe Hemorrhage (TASH) score[29] and the Assessment of Blood Consumption (ABC) score,[30] have been developed to predict the probability of massive transfusion after major trauma, but both seem unwieldy for practical use in the ED.

Is a Blood Substitute on the Horizon?

Source: Natanson C, Kerns SJ, Lurie P, et al. Cell-free hemoglobin-based blood substitutes and risk of myocardial infarction and death: A meta-analysis. JAMA 2008;299:2304-2312.

Hemoglobin-containing blood substitutes have been advocated as an alternative to blood component transfusion.[31] (*See Table 3.*) These solutions have been touted as having several advantages over blood components, including long shelf life, no need for refrigeration or cross-matching, and absence of infection risk. Several trials using these products have failed to demonstrate a clinical benefit, but the significant advantages and limited risks have encouraged more trials comparing these solutions to blood components. Despite the different biochemical properties of several preparations, all contain hemoglobin, which has been shown to cause systemic vasoconstriction, decreased blood flow, increased release of pro-inflammatory mediators and potent vasoconstrictors, and a loss of platelet inactivation,[32-35] creating conditions that may lead to vascular thrombosis of the heart or other organs. This meta-analysis was conducted to determine if there was a risk of myocardial infarction (MI) and death associated with blood substitute use.

A literature search was conducted to find all randomized clinical trials involving hemoglobin-based blood substitutes. In addition to traditional medical databases, other sources included product press releases and FDA analyses. Treatment and control groups were compared for the risk of myocardial infarction and death.

Sixteen trials of five distinct hemoglobin-based blood substitutes (HBBS) were included in the analysis. Eleven of the trials were either double-blinded or single-blinded studies. There were 164 deaths in the heme-substitute group and 123 deaths in the controls. Overall, HBBS products were associated with a significantly increased risk of death (RR, 1.30; 95% CI, 1.05-1.61). There was a total of 59 MIs in the HBBS-treated patients and 16 MIs in the patients in the control groups. There was a significant increase in the risk of MI among patients receiving HBBSs (RR, 2.71; 95% CI, 1.67-4.40). This translated into one death for every 62 patients treated and one MI for each 50 patients treated with hemoglobin-based blood substitutes. Unpublished data reviewed by the authors confirmed the elevated risk of death and MI.

Comment. This meta-analysis appears to demonstrate some clinically important clinical risks associated with the use of hemoglobin-based blood substitutes. This risk is demonstrated to be statistically as well as clinically relevant remembering that there are limitations inherent in meta-analysis as a research approach. The obvious concern with "pooling" these studies is whether a small subgroup accounts for the vast majority of the risk. In addition, it is possible that as each formulation of the hemoglobin-based preparation is refined that the risks will diminish over time.

The inevitable conclusion, however, is that as persistent risk appears to be demonstrated with the use of these products, it is less likely that further testing will occur. These products have significant theoretical appeal, including ease of storage and administration, low risk of infection,

Table 3: Status of Hemoglobin-based Blood Substitutes

Product	Company	Hemoglobin source	Chemical alteration	Percent intact hemoglobin tetramer	Current status (2010)
HemAssist®	Baxter Healthcare	Human	Diaspirin cross-linking	99%	Further development halted in 1998
Hemolink®	Therapure Biopharma Inc. (formerly Hemosol BioPharma Inc.)	Human	Polymerization	30-40%	Further development halted in 2007
Hempure®	OPK Biotech (previously known as Biopure Corp.)	Bovine	Pyridoxylation	< 5%	No longer available as of December 2009
Hemospan®	Sangart Inc.	Human	Pegylation	100%	Phase IIa clinical trial started in Europe and South Africa in December 2009
PolyHeme®	Northfield Laboratories Inc.	Human	Polymerization	≤ 1%	Company filed for Chapter 11 bankruptcy in June 2009 with plans to liquidate its remaining assets
Hemoximer® (PHP or Pyridoxalated Hemoglobin Polyoxyethylene)	Apex Bioscience (now a wholly-owned subsidiary of Curacyte AG)	Human	Pyridoxylation	≤ 0.5%	Phase III clinical trial started in Europe in June 2009

and particular utility in prehospital and rural settings. However, studies evaluating side-effects of these preparations have repeatedly demonstrated a limited future in trauma resuscitation.

Is There a Role for Antifibrinolytic Therapy to Limit Hemorrhage After Major Trauma?

Source: CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): A randomised, placebo-controlled trial. Lancet 2010 Jun 14. [Epub ahead of print]

The hemostatic system is activated in response to endothelial damage, with the formation of blood clots (to limit blood loss) and the activation of the fibrinolytic system (to limit the extent of intravascular clotting and maintain microvascular perfusion). Major trauma can trigger widespread hemostatic activity so that the appropriate fibrinolytic response can become excessive, even pathologic (hyper-fibrinolytic). This concept that inhibiting fibrinolytic activity may reduce blood loss has been studied in patients undergoing major surgery. A systematic review of 53 trials of patients undergoing elective surgery — randomized to placebo or tranexamic acid (an antifibrinolytic agent) — found that tranexamic acid reduced blood transfusions by about a third.[36] Tranexamic acid — a synthetic modification of the amino acid lysine — blocks lysine-binding sites on the plasminogen molecule, preventing the conversion to plasmin and thus inhibiting fibrinolysis.

The concept that an early administration of a short course of tranexamic acid can reduce death in trauma patients was tested in the CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2) trial. This was a large placebo-controlled, multinational (274 hospitals in 40 countries) trial that started in 2005. Adult trauma patients within 8 hours of injury and with significant hemorrhage (systolic blood pressure < 90 mmHg or heart rate >110 beats per min, or both), or who were considered to be at risk of significant hemorrhage were eligible for enrollment. Tranexamic acid was administered as a 1 g loading dose infused over 10 min, followed by an additional 1 g infused over 8 h (125 mg/h). A total of 20,211 patients were initially randomized and data on 10,060 in the tranexamic acid and 10,067 in the placebo group were available for

analysis on an "intention-to-treat" basis.

Tranexamic acid use was associated with a significant reduction in both overall mortality (14.5% vs. 16.0%, relative risk 0.91, 95% CI 0.85-0.97; p = 0.0035) and death due to bleeding (4.9% vs. 5.7%; relative risk 0.85, 95% CI 0.76-0.96; p = 0.0077) during the 4 weeks after injury. There was no difference in deaths due to vascular occlusive events (pulmonary embolus, deep venous thrombosis, or myocardial infarction), multi-organ failure, or other causes. Prespecified subgroup analysis found no evidence of heterogeneity with stratification according to systolic blood pressure, Glasgow Coma Score at time of randomization, type of injury, or time from injury to randomization.

In the article and an accompanying editorial,[37] it is noted that plasmin has more effects than just fibrinolysis. Plasmin can enhance the activation of prothrombin to thrombin and proteolyze platelet receptors (including glycoprotein Ib and IIb/IIIa). Plasmin also has pro-inflammatory effects by binding and activating monocytes, neutrophils, platelets, endothelial cells, and complement-releasing lipid mediators and cytokines, and by inducing pro-inflammatory genes. Therefore, the observed beneficial effect of tranexamic acid may be due to a moderation of the pathologic activation of the coagulation and inflammatory systems seen in major trauma.

Comment. The rationale for this study was that traumatic injuries are an increasing cause of death in the developing world and that hemorrhage is responsible for about a third of all in-hospital deaths. This study was designed to use a fixed dose of a generic medication that could be easily administered in a wide variety of hospitals. The study enrolled the majority of patients from Africa, South American, and Asia, with less than 10% from Western Europe or North America (none from the United States). While not specifically commented upon, the logistical difficulties with blood transfusion in these developing countries is perhaps reflected in the report that only about half of the study patients received a blood product transfusion, with a median of only 3 (IQR 2 to 6) units of blood products administered in these patients. Likewise, only about 48% of all patients underwent some surgical procedure.

It is hard to criticize such a large multinational study with a clearly defined outcome; the patient was either alive or dead. The authors rightly note that the diagnosis of hemorrhage was a clinical one, but felt that was appropriate because the results could be widely applicable from small rural hospitals to large urban ones. The diagnosis of vascular occlusive events required clear clinical evidence so that, while specificity for this occurrence was felt to be high, sensitivity was probably low, and it is possible that these events were under-reported. For physicians in the United States, it is difficult to evaluate the potential benefits of tranexamic acid in their practice, considering the low rate and quantity of blood transfusion observed in this study compared to the ready availability of large amounts of blood products for use in treating hemorrhage in U.S. hospitals.

The authors advocate that tranexamic acid should be considered for inclusion on the WHO List of Essential Medicines. This WHO document is designed to provide a "list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment."[38] Given the low cost of tranexamic acid (the estimated international price was $13 per 2 g dose in 2007) and the higher cost of blood transfusion, tranexamic acid was judged to be highly cost-effective in preventing death from surgical bleeding in four different African countries.[39] It is likely that antifibrinolytic therapy to prevent death of surgical and traumatic bleeding will be most useful in these developing countries.

Where Do We Stand Regarding Transfusion Therapy for Major Trauma in 2010?

Acidosis, hypothermia, and coagulopathy are the enemy of emergency physicians and trauma surgeons who provide early stabilization of the trauma patient. Acidosis can be addressed by early aggressive resuscitation, whereas hypothermia is managed by protecting the patient from cool temperatures in the environment and resuscitation fluids used. Coagulopathy is likely multifactorial and may exist in 25% of patients before arrival in the resuscitation suite. Whole blood has been shown to effectively prevent the development of coagulation disorders in the combat environment,[1,2] and more recent retrospective studies[40,41] support a relationship between better outcomes and near "physiologic" ratios of red blood cells, plasma, and platelets. Many large trauma centers have adopted resuscitation protocols that mimic whole blood transfusions in those injured patients who are considered to be at risk for massive blood loss. However, this practice has not been universally accepted. A recent survey found that only 45% of trauma centers have adopted a massive transfusion protocol.[42] In addition, the implementation of near physiologic ratios of packed RBC, fresh frozen plasma, and platelets puts additional strain on the already taxed blood supply. Confirmation of the benefits of increased FFP:RBC or platelet:RBC must await good prospective trials.

Alternatives to blood component therapy in the form of hemoglobin-based blood solutions have been available in several formulations for years. They have many theoretical advantages over blood components and could potentially replace crystalloid infusions in the prehospital setting. Studies utilizing blood substitutes have shown significant risk

of both death and myocardial infarction. Further refinements of these products may eventually lead to a clinically viable product with limited morbidity and mortality. However, clinical use of such products appears to be in the distant horizon.

Lastly, the concept of antifibrinolytic therapy to reduce death following major trauma is very intriguing but will require further study before it becomes an accepted modality. The results of the CRASH-2 trial cannot be extrapolated to other, usually larger, doses of tranexamic acid, other antifibrinolytic agents, or settings with robust transfusion resources.

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Physician CME Questions

11. What is the leading cause of preventable death from trauma?
    A. multi-organ failure
    B. sepsis
    C. hemorrhage
    D. respiratory arrest

12. Which injuries are particularly prone to develop coagulopathy?
    A. brain injury and long bone fractures
    B. hepatic and splenic injuries
    C. intestinal and renal injuries
    D. pulmonary and cardiac injuries

13. Which of the following statements regarding the hemoglobin level for a red blood cell transfusion trigger is *not* true?
    A. Most patients will benefit from transfusion at a level < 6 g/dL.
    B. Some patients will benefit from transfusion at a level > 8 g/dL.
    C. Few patients will benefit from transfusion at a level > 10 g/dL.
    D. Most patients will benefit from transfusion at a level < 8 g/dL.

14. Which of the following statements is true regarding platelet transfusion in the trauma patient with microvascular bleeding?
    A. Platelets should be transfused if the platelet count is < 50,000/mm^3.
    B. Platelets should not be transfused in patients with a disorder that causes platelet dysfunction.
    C. Platelets should be routinely transfused if the platelet count is < 100,000/mm^3.
    D. Prophylactic transfusion is usually effective.

15. Which of the following statements is true regarding the aggressive use of FFP and platelets in patient undergoing massive transfusion (more than one unit of FFP or platelets to every two units of PRBC)?
    A. An increased incidence of multisystem organ failure has been observed in patients receiving aggressive FPP and platelet transfusions.
    B. An increased 30-day survival has been observed in patients with truncal trauma.
    C. An increased 30-day survival has been observed in patients with head injury.
    D. No difference in survival has been observed in patient receiving aggressive FFP and platelet transfusions.

16. Which of the following is *not* a claimed benefit of a proactive trauma exsanguination or massive transfusion protocol?
    A. improved 30-day survival
    B. reduced rate of severe sepsis and septic shock
    C. reduced rate of multi-organ failure
    D. reduced rate of renal failure

17. Which statement is true regarding the transfusion of one unit of FFP along with each unit of PRBC in patients with traumatic injury?
    A. It is associated with improved survival in all patients.
    B. It is associated with improved survival only if more than 10 units of PRBC are transfused.
    C. It is associated with improved survival in patients with penetrating truncal trauma.
    D. It is associated with improved survival in patients with blunt hepatic trauma.

18. Which of the following is *not* an independent predictor of the requirement for massive transfusion?
    A. administration of uncross-matched blood in the ED
    B. initial systolic BP < 90 mmHg
    C. blunt abdominal trauma
    D. severe injury (Injury Severity Score ≥ 20)

19. Hemoglobin-based blood substitutes are associated with an increased risk of myocardial infarction and death in trauma patients.
    A. true
    B. false

20. Which of the following statements concerning the early use of tranexamic acid in patients with trauma and severe hemorrhage was observed in the CRASH-2 study?
    A. increased rate of vascular occlusive events
    B. reduced all-cause mortality rate
    C. increased incidence of multi-organ failure
    D. reduced mortality rate from head injury

CME Answer Key

11. C; 12. A; 13. D; 14. A; 15. B; 16. D; 17. B; 18. C; 19. A; 20. B

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The Coagulopathy of Major Trauma and Massive Transfusion

Consensus-based Transfusion Triggers

Product	
Packed RBCs	• Almost always indicated when hemoglobin < 6 g/dL • Clinical assessment of perfusion and oxygen delivery are used to determine if RBC transfusion is indicated with hemoglobin between 6 and 10 g/dL. • Rarely indicated when hemoglobin > 10 g/dL
Platelets	• Prophylactic platelet transfusion is generally ineffective. • Platelet transfusion rarely effective when thrombocytopenia is due to increased platelet destruction or consumption. • Trauma patients with microvascular bleeding usually require regular platelet transfusions when the platelet count is < 50,000/mm^3. • Assessment of risk for serious hemorrhage should be used to determine if platelet transfusion is indicated in trauma patients with microvascular bleeding when the platelet count is between 50,000 and 100,000/mm^3. • Trauma patients with microvascular bleeding rarely benefit from platelet transfusion when the platelet count is > 100,000/mm^3. • Platelet transfusion may be useful in patients with a known disorder of platelet function and microvascular bleeding, even if the platelet count is normal.
Fresh Frozen Plasma (FFP)	• Indicated for control of microvascular bleeding when the PT or aPTT is > 1.5 times control. • Indicated for control of microvascular bleeding in patients undergoing massive transfusion.
PT = prothrombin time; aPTT = activated partial thromboplastin time	

Status of Hemoglobin-based Blood Substitutes

Product	Company	Hemoglobin source	Chemical alteration	Percent intact hemoglobin tetramer	Current status (2010)
HemAssist®	Baxter Healthcare	Human	Diaspirin cross-linking	99%	Further development halted in 1998
Hemolink®	Therapure Biopharma Inc. (formerly Hemosol BioPharma Inc.)	Human	Polymerization	30-40%	Further development halted in 2007
Hempure®	OPK Biotech (previously known as Biopure Corp.)	Bovine	Pyridoxylation	< 5%	No longer available as of December 2009
Hemospan®	Sangart Inc.	Human	Pegylation	100%	Phase IIa clinical trial started in Europe and South Africa in December 2009
PolyHeme®	Northfield Laboratories Inc.	Human	Polymerization	≤ 1%	Company filed for Chapter 11 bankruptcy in June 2009 with plans to liquidate its remaining assets
Hemoximer® (PHP or Pyridoxalated Hemoglobin Polyoxyethylene)	Apex Bioscience (now a wholly-owned subsidiary of Curacyte AG)	Human	Pyridoxylation	≤ 0.5%	Phase III clinical trial started in Europe in June 2009

Sample of a Massive Transfusion Protocol

Initial transfusion	• 10 units of type O packed RBCs (Rh-negative in females < 50 years old) • 6 units of type AB/Rh-negative FFP • 2 units of single-donor apheresis platelets
Subsequent transfusions	• 6 units of cross-matched or type-specific packed RBCs • 6 units of type-specific FFP • 1 unit of single-donor apheresis platelets

Supplement to *Emergency Medicine Reports*, July 5, 2010: "The Coagulopathy of Major Trauma and Massive Transfusion." *Authors:* **Howard A. Werman, MD, FACEP,** Professor of Emergency Medicine, Ohio State University, Columbus; and **Robert Falcone, MD, FACS**, Clinical Professor of Surgery, Ohio State University, Columbus.