DAMAGE CONTROL RESUSCITATION

Chapter 4

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Table of Contents

Introduction

Hemorrhage accounts for 30 to 40 percent of all fatalities, second only to traumatic brain injury as a cause of death following trauma.[1,2,3] Hemorrhagic death is the leading preventable cause of mortality in combat casualties and typically occurs within six to 24 hours of injury.[4,5,6,7,8,9,10] Patients who die from hemorrhage enter a "vicious bloody cycle" characterized by the lethal triad of hypothermia, acidosis, and coagulopathy.[11]

> Hemorrhagic death is the leading preventable cause of mortality in combat casualties and typically occurs within six to 24 hours of injury. Causes of death from massive hemorrhage include compressible extremity hemorrhage (due to amputation or vascular injury), noncompressible proximal extremity hemorrhage (axillary or groin vascular injuries), and truncal hemorrhage (from solid organ, pelvic fracture, and thoracic injuries).

Damage control resuscitation (DCR) is a strategy that seeks to prevent or mitigate hypothermia, acidosis, and coagulopathy through combined treatment paradigms. Damage control resuscitation comprises early hemorrhage control, hypotensive resuscitation (permissive hypotension), hemostatic resuscitation (minimization of crystalloid fluids and fixed ratio blood product transfusion), prevention or alleviation of hypothermia (through warming measures), and amelioration of acidosis through judicious use of blood products and hemodynamic resuscitation endpoints.[12,13,14,15,16] In short, the goal of DCR is to stop hemorrhage and prevent or reverse the three components of the lethal triad.

The majority of trauma patients arriving at hospitals in both civilian and military settings will not require transfusion and are not coagulopathic on arrival. However, an important subset of severely injured casualties will manifest coagulopathy on arrival.[17,18] These patients are more likely to require massive transfusion, defined as infusion of 10 or greater units of red blood cells (RBCs), in the first 24 hours following injury. Traumatic coagulopathy exacerbates bleeding from injury, and aggressive resuscitation can cause patients to spiral into the "bloody vicious cycle" in which coagulopathy leads to further hemorrhage and worsening
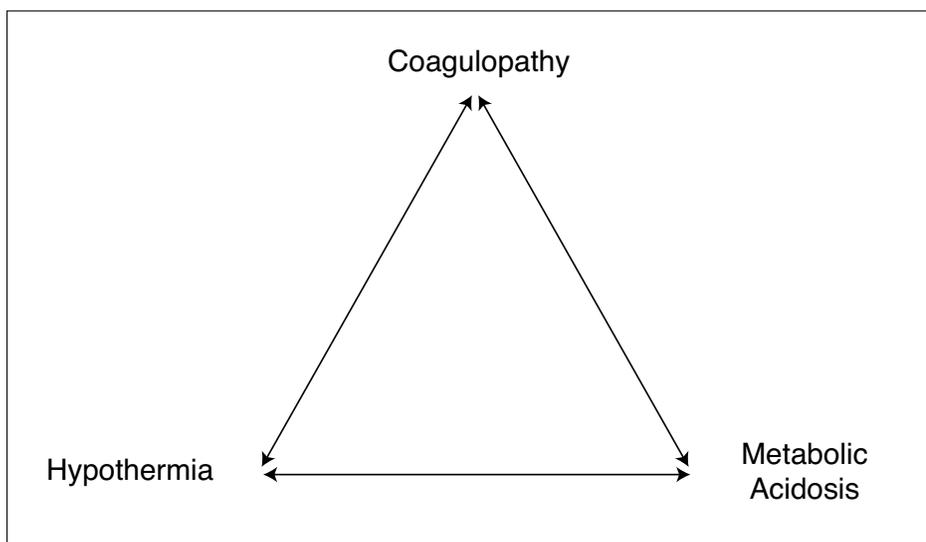

Figure 1. *The lethal triad.*

acidosis, in turn prompting additional fluid resuscitation and transfusion (Fig. 1). Such resuscitation can then contribute to more profound coagulopathy resulting from hemodilution and hypothermia. When such coagulopathy is present, it is associated with increased mortality.[17,18] Acidosis, hypothermia, and coagulopathy have been collectively termed the "lethal triad."[19]

Massive transfusion is defined as infusion of 10 or greater units of RBCs in the first 24 hours after injury. Massive blood transfusion is infrequent in civilian trauma, occurring in only 2 to 13 percent of trauma admissions. Due to a higher rate of penetrating injury in combat casualties, massive transfusion occurred in approximately 8 percent of OIF casualties.

Causes of death from massive hemorrhage include compressible extremity hemorrhage (due to amputation or vascular injury), noncompressible proximal extremity hemorrhage (axillary or groin vascular injuries), and truncal hemorrhage (from solid organ, pelvic fracture, and thoracic injuries).[5] Patients with the aforementioned injuries may benefit from DCR in parallel with damage control surgical management.[5] Both damage control strategies are used to treat the acute traumatic problems of hemorrhage and coagulopathy. They are intended to prevent the complications that can occur following extensive operations and infusion of large volumes of fluids and blood products.

DCR LESSONS LEARNED IN OEF AND OIF AS OF 2010

- Rapid control of compressible hemorrhage should be initiated with direct pressure, tourniquets, or hemostatic dressings.
- There should be rapid identification and surgical control of noncompressible and major vascular hemorrhage sites.
- The use of crystalloid and colloid solutions should be minimized in hemodynamically stable patients.
- Patients requiring DCR should be identified early using rapid bedside measures or tests.
- The early delivery of plasma and platelet transfusion in fixed ratios to red blood cells approaching 1:1:1 should be considered.
- Until surgical control of bleeding has been achieved, continued transfusion should be based primarily on the clinical condition of the patient rather than on laboratory values.
- Advanced bedside coagulation studies (e.g., thromboelastography) are available at some Level III care facilities and may provide better guides to a patient's blood product needs than standard laboratory values such as prothrombin time (PT) and activated partial thromboplastin time (aPTT).
- The use of low-dose vasopressin and other vasopressors as an adjunct to DCR is a treatment option that requires further validation.
- Adjuncts for control of nonsurgical bleeding (e.g., recombinant factor VIIa or antifibrinolytics) can be considered but remain controversial.
- Damage control resuscitation can be terminated once clinical hemorrhage is controlled and validated endpoints of resuscitation, such as clearance of serum lactate or base deficit, have been achieved.

Table 1. *DCR lessons learned in OEF and OIF.*

Damage Control Resuscitation: Lessons Learned

This chapter will address the key components of DCR, including: (1) preventing the need for massive transfusion through external hemorrhage control to prevent exsanguination; (2) predicting the need for massive transfusion of blood products; (3) current recommendations for massive transfusion and management of the anticipated complications; and (4) adjuncts to resuscitation and transfusion that are frequently employed in damage control settings. An overview of DCR lessons learned over the course of Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) is provided in Table 1.

Preventing the Need for Massive Transfusion

Ideally, traumatic hemorrhage is controlled prior to hemodynamic compromise resulting from exsanguination. A series of preventive measures and prehospital treatment techniques have been instituted in both military and civilian trauma settings to rapidly control hemorrhage. The tools and techniques discussed below may prevent or slow ongoing blood loss, decrease the number of blood products required, and ultimately prevent unnecessary deaths.

Hemorrhage Control Techniques

Hemorrhage sites are either anatomically compressible and amenable to tourniquet control, compressible but not amenable to tourniquet control (e.g., axillary or groin vascular injuries), or completely noncompressible (e.g., truncal injuries) (Fig. 2). Patients with noncompressible hemorrhage sources should receive the highest priority for evacuation to a hospital, as there are few tools available to prehospital careproviders to manage such bleeding. Compressible hemorrhage sites are amenable to direct digital pressure, which can be instituted by first responders as the initial hemorrhage control intervention. Attempts to reinforce saturated dressings with large stacks of gauze or additional dressings (in lieu of manual compression) should be avoided, as this technique dissipates the pressure applied directly to the bleeding site and may delay identification of ongoing bleeding (Fig. 3).

> Hemorrhage sites are either anatomically compressible and amenable to tourniquet control, compressible but not amenable to tourniquet control (e.g., axillary or groin vascular injuries), or completely noncompressible (e.g., truncal injuries). Tourniquet application, direct pressure, or hemostatic dressings applied to the wound site should be favored over pressure point control and extremity elevation for the initial control of hemorrhage.

Direct pressure to arteries proximal to bleeding sites and elevation of the affected extremity above the level of the heart should be considered as second-line adjunctive hemorrhage control interventions, and they are not currently recommended for use by the Committee on Tactical Combat Casualty Care for any phases of care.[20] Applying direct pressure to the arteries proximal to the bleeding site may control arterial inflow, but it will not control venous hemorrhage. Associated injuries (e.g., fractures) and patient transportation considerations often make extremity elevation problematic. Hence, tourniquet application, direct pressure, or hemostatic dressings applied to the wound site should be favored over pressure point control and extremity elevation for the initial control of hemorrhage.[21]

Hemorrhage Pressure Points

Wound of neck

Wound of lower face (below eyes)

Wound of lower part of upper arm and elbow

Wound of lower arm

Wound of hand

Wound of thigh
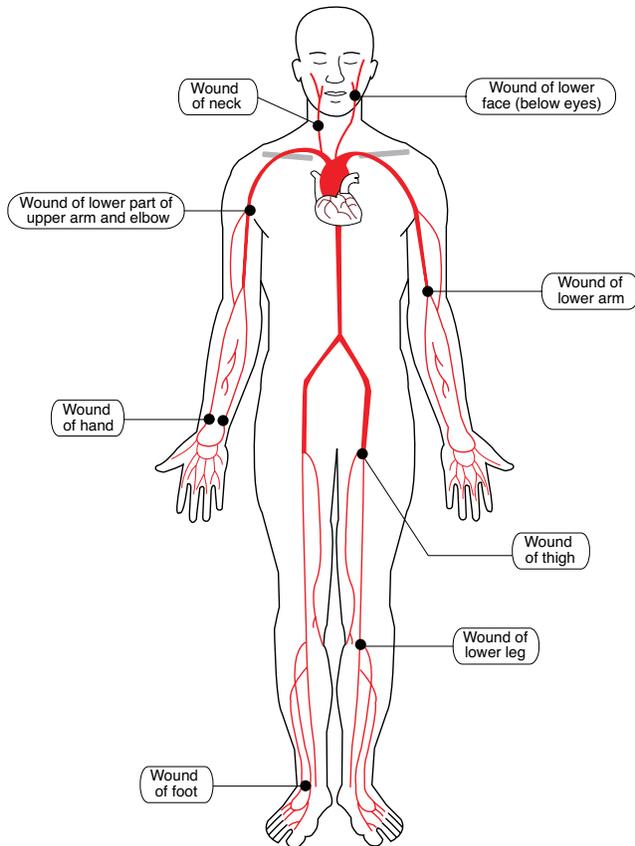
Wound of lower leg

Wound of foot

Figure 2. (Left) *Potential sites for pressure point control of hemorrhage.*

Figure 3. (Below) *A combat casualty arriving at a Level III facility following a fragmentation injury from a blast. Note the saturated layers of gauze on this limb where no tourniquet or hemostatic agents was applied.*

Tourniquets and Hemostatic Dressings

The use of direct pressure to control hemorrhage is only a temporizing measure until a more secure and durable form of hemorrhage control can be employed. First responders often find it necessary to perform other tasks or treat other casualties; hence, modular tourniquets and hemostatic dressings have been developed to provide the first responder with alternative methods for hemorrhage control.

Historically, extremity tourniquets were a controversial method of last resort for extremity hemorrhage control.[22,23] Extremity tourniquets are now used as a first-line therapy for the prehospital control of extremity hemorrhage for care-under-fire scenarios (Fig. 4).[20] Expanded guidelines for tourniquet use, combined with a rapid evacuation system in OEF and OIF, have resulted in significant numbers of casualties arriving to surgical care with extremity tourniquets in place (Fig. 5). Multiple reports in the literature of tourniquet use in OEF and OIF have defined the characteristics and advantages of tourniquet use.[16, 24,25,26,27,28] These include: (1) an average prehospital tourniquet time under six hours; (2) improved hemorrhage control upon patient arrival; (3) decreased incidence of shock in those casualties treated with tourniquets; (4) improved survival; and (5) acceptably low tourniquet-related complications. Tourniquets should be applied to exsanguinating extremities as soon as possible in care-under-fire scenarios.[29] Additional information on tourniquets can be found in the Extremity Injury chapter.

Figure 4. (Right) *The Combat Application Tourniquet® is a one-handed tourniquet that uses a self-adhering band to fit a wide range of extremities. It incorporates a windlass system that locks into place. Image courtesy of North American Rescue, LLC.*

Figure 5. (Below) *A combat casualty who sustained bilateral lower extremity injuries from an improvised explosive device (IED) blast with right-sided tourniquet in place.*

> Extremity tourniquets are used as a first-line therapy for the prehospital control of extremity hemorrhage in care-under-fire scenarios. If used before onset of shock, there is 90 percent improved survival relative to use after onset of shock. Hemostatic dressings and agents are used with increased frequency, as both primary hemorrhage control measures for wounds not amenable to tourniquet control or as adjuncts to tourniquet use.

Similarly, hemostatic dressings and agents are now deployed and used with increasing frequency as both primary hemorrhage control measures for wounds not amenable to tourniquet control or as adjuncts to tourniquet use.[20,21] Animal research demonstrates the superiority of dressings such as the fibrin-impregnated bandage (produced by the American Red Cross) and chitosan dressings over standard gauze.[30] Another agent, granular zeolite [QuikClot® (Z-Medica; Wallingford, CT)], a microporous crystalline aluminosilicate hemostatic agent, is Food and Drug Administration (FDA) approved for hemostasis of external wounds (Fig. 6). Granular zeolite has been fielded by the United States (US) Marine Corps and US Army during OEF and OIF with some success.[31,32] Limitations of granular zeolite include an exothermic reaction that can cause burns, and the time-consuming removal of granules from wounds. The potential utility of these dressings has been supported by early clinical reports from OEF and OIF.[31,33]

Figure 6. *This Iraqi civilian was injured by a blast fragment. The blast fragment caused a through-and-through injury to the proximal left arm causing hemorrhage that was not amenable to tourniquet use. Hemorrhage was controlled with QuikClot®. Image courtesy of Harold Bohman, MD, CAPT, MC, US Navy.*

The challenge of developing and fielding newer generations of bandages is illustrated by the recall of a granular combination of a smectite mineral and polymer in 2008 (WoundStat™ [TraumaCure, Inc; Bethesda, MD]) due to concerns over the risk of thrombosis and endothelial injury when applied to arteries. This agent had been tested by the US Army Institute of Surgical Research (USAISR) and had been shown to be more efficacious in treating animal models of arterial hemorrhage than currently deployed products.[34] Combat Gauze™ (Z-Medica, Wallingford, CT) is composed of surgical gauze impregnated with kaolin (Fig. 7). This dressing has been shown to be extremely safe and effective in a lethal animal hemorrhage model.[35] Combat Gauze™ is the current hemostatic dressing of choice for the military as recommended by the Committee on Tactical Combat Casualty Care.[20] It is important to note that clinical experience with Combat Gauze™ is limited, and there are currently no publications on its use in humans. Further clinical experience with hemostatic agents and dressings will be required to fully define their clinical benefits and risks.

Figure 7. *Combat Gauze™, a kaolin-impregnated surgical gauze, is the current hemostatic dressing of choice. The gauze is tightly packed into the wound, then pressure is held directly over the bleeding source until hemorrhage stops. Image courtesy of Combat Medical Systems™.*

Preventing Hypothermia

Hypothermia is defined as mild when the core body temperature is 32°C to 35°C, moderate when the core body temperature is 28°C to 32°C, and severe when the core body temperature is below 28°C.[36] Hypothermia is associated with an increased risk of uncontrolled bleeding and mortality in trauma patients.[36,37] Severe trauma-related hypothermia has been associated with 100 percent mortality.[38] Trauma patients in hemorrhagic shock have uncoupling of normal metabolic pathways, resulting in the loss of the ability to maintain temperature homeostasis. Factors such as cold or wet weather, prolonged extrication or scene time, intoxication, infusion of cold or room temperature fluids, and convective heat losses (e.g., open helicopter door during flight) can worsen hypothermia. Both civilian and military trauma centers have linked the presence of hypothermia on arrival to increased mortality.[39,40,41]

Hypothermia in combat casualties was identified as a theater-wide trauma system challenge in OIF.[42,43] Simple hypothermia prevention measures were disseminated to the combat medics on the battlefield. These measures included emphasis on external hemorrhage control as the first priority, limiting removal of clothing to areas of the body requiring treatment, wrapping casualties in wool or solar blankets, and using in-line fluid warmers such as the Thermal Angel® (Estill Medical Technologies, Inc., Dallas, Texas) (Fig. 8).

Figure 8. (Above) *A combat casualty arriving at a Level III facility. Hypothermia prevention measures include wrapping the casualty in wool and solar blankets, and limited removal of clothing.*

Figure 9. (Right) *Active rewarming and stabilization of the patient in an intensive care unit (ICU) using a solar blanket, warmed fluids, and a warm humidified ventilator circuit. Image courtesy of the Borden Institute, Office of The Surgeon General, Washington, DC.*

> Prevention and treatment of hypothermia at initial care facilities include the use of standardized heat-loss prevention kits, forced-air warming blankets, fluid warmers and rapid infusers, maintenance of warmed trauma suites and operating rooms, and warm humidified ventilator circuits.

Measures to prevent and treat hypothermia at initial care facilities have included the use of standardized heat-loss prevention kits (e.g., solar blankets, heated blankets, and body bags), the use of forced-air warming blankets, the use of fluid warmers and rapid infusers, the maintenance of warmed trauma suites and operating rooms, and the use of warm humidified ventilator circuits (Fig. 9).[15,44,45,46,47,48,49] Since institution of these performance improvement measures, the incidence of hypothermia in patients arriving at Combat Support Hospitals (CSHs) has fallen from 7 percent to below 1 percent.[43] Since severe hypothermia has become a rarity in OEF and OIF, active core body rewarming measures, such as continuous arteriovenous rewarming and body cavity lavage of warmed fluids, are less frequently needed.[50,51] While cardiopulmonary bypass may be used in extreme cases of hypothermia for controlled active rewarming in some civilian trauma centers, it is not available in Level III care facilities in Iraq or Afghanistan.

Predicting the Need for Massive Transfusion

Despite marked advances in the prehospital management of hemorrhage, patients with noncompressible sources of bleeding will still arrive in the trauma bay with uncontrolled hemorrhage. Effective DCR often requires the early delivery of coagulation factors, soon after patient arrival to the resuscitation area.[4] Since coagulation factor replacement is needed by only a small fraction of trauma patients, rapid identification of such patients is critical.[4,52] Clinical and laboratory parameters are used to predict the need for massive transfusion in such patients.[53]

> Penetrating mechanisms of injury, particularly involving the trunk, predict the need for massive transfusion in combat casualties. Systemic hypotension is a useful and validated predictor for the need for both emergent intervention and transfusion in the arriving trauma patient.

Mechanism of Injury

Penetrating mechanisms, particularly involving the trunk, predict the need for massive transfusion in

Figure 10. *This host national was admitted to a CSH with hypotension and multiple fragment entry wounds to his chest and abdomen. This patient is at elevated risk for requiring massive transfusion. Image courtesy of the Borden Institute, Office of The Surgeon General, Washington, DC.*

combat casualties and for emergent intervention in civilian trauma patients (Fig. 10).[52,54] This contrasts with blunt mechanisms of injury, which are poor predictors of the need for trauma team activation or emergent intervention.[54,55] The presence of penetrating wounds in combat casualties is frequently obvious and dramatic, as with high-velocity penetrating abdominal wounds with associated evisceration, multiple proximal limb amputations, and penetrating buttock or pelvic wounds (Fig. 11). Combat casualty care (CCC) providers are usually able to visually appreciate the extent of tissue destruction and anticipate associated anatomic and physiologic derangements in such casualties.

Bedside Clinical Findings

Heart rate alone is an insufficient predictor of the need for emergency interventions for management of hemorrhage.[56] A core body temperature below 36°C (96°F) on arrival has been shown in both civilian and military trauma patients to be associated with worse outcomes.[39,41,57] Furthermore, several investigators have correlated the presence of hypothermia with injury severity and the requirement for blood transfusion.[58,59,60]

Systemic hypotension is a useful and validated predictor of the need for both emergent intervention and

Figure 11. *Host national who sustained a blast injury to his flank with traumatic evisceration. Image courtesy of the Borden Institute, Office of The Surgeon General, Washington, DC.*

transfusion in the arriving trauma patient.[54,61,62,63] Systolic blood pressure has been combined with other variables to create trauma scores, such as the Revised Trauma Score (RTS).[64,65,66,67] Although not perfect, these scores are superior to any single test alone and have emerged as useful and accurate predictors of mortality and the requirement for massive transfusion.[68] Rapid manual bedside tests such as the radial pulse character and Glasgow Coma Scale (GCS) motor score have also been shown to predict the need for lifesaving interventions.[69] In Holcomb's study, trauma patients with a weak or absent radial pulse combined with an abnormal GCS verbal or motor score on arrival had an 88 percent probability of requiring a lifesaving intervention.[69] On the basis of simplicity, rapidity, and relative accuracy, these techniques are helpful in both the prehospital and initial hospital management of trauma patients.[69,70]

While hypotension historically has been defined as a systolic blood pressure (SBP) below 90 mm Hg, recently this value has been challenged. Eastridge and colleagues recently evaluated data from the National Trauma Data Bank and found that an admission SBP value below 110 mm Hg was associated with higher mortality rates.[71] Every 10 mm Hg drop in SBP below 110 mm Hg was associated with a 4.8 percent increase in mortality, up to a maximum of 26 percent mortality at a systolic blood pressure of 60 mm Hg. The authors also noted that base deficits began to rise below a SBP of 118 mm Hg. These findings imply that some trauma patients may have systemic tissue hypoperfusion despite systolic blood pressures well above 90 mm Hg.

Laboratory Testing

The role of clinical laboratory testing in predicting the need for massive transfusion remains in evolution. Admission labs associated with the need for massive transfusion include a base deficit greater than six, an international normalized ratio (INR) of 1.5 or greater, and a hemoglobin value of less than 11 grams (g) per deciliter.[52,72,73] In a more recent study, McLaughlin et al. found that a heart rate greater than 105 beats per minute, a SBP less than 110 mm Hg, a pH value less than 7.25, and a hematocrit value of less than 32 percent were all independent predictors of massive transfusion in combat casualties.[74] This preliminary study awaits further validation. Patients with any of these values, particularly in combination with hypotension, diminished GCS score, or obvious physical exam findings, should be considered for immediate transition from a standard resuscitation mode to a damage control resuscitation mode.[63]

> Admission labs associated with the need for massive transfusion include a base deficit greater than six, an international normalized ratio of 1.5 or greater, and a hemoglobin value of less than 11 g per deciliter. Such laboratory tests are generally available at Level II facilities.

Laboratory tests generally available at Level II facilities (Forward Surgical Teams and Forward Resuscitative Surgical Systems) include arterial blood gas, complete blood count analysis, PT and INR. At Level III facilities, PT and INR are routinely available, and even thromboelastography is available at some CSHs in Iraq and Afghanistan. Thromboelastography provides real-time graphic evidence of clot formation in whole blood and may be a better method of detecting coagulopathy in trauma patients.[75,76]

Newer Technologies for Predicting the Need for Massive Transfusion

The utility of novel applications of continuous, noninvasive monitors linked to computer software are under study as tools to provide an early warning of systemic hypoperfusion. These technologies include the measure of heart rate complexity, arterial pulse pressure, and tissue oxygenation as measured by near-

infrared spectroscopy.[77,78,79,80,81,82,83,84] Loss of heart rate variability has predicted the need for lifesaving interventions and increased mortality in trauma patients.[85,86,87] Decreased tissue oxygen saturation detected by continuous near-infrared spectroscopy has predicted the development of multiple organ failure and the need for massive transfusion.[88] While these technologies will not replace clinical judgment, they may add objective data to help careproviders maximize patient outcomes while minimizing resource utilization.

Transfusion of Blood Products

For most casualties, current resuscitation guidelines published in the American College of Surgeons Advanced Trauma Life Support (ATLS) course and elsewhere are sufficient for managing blood and fluid losses. However, the frequent need for massive transfusion of blood products in OEF and OIF has prompted critical reassessment of the appropriateness of these standard resuscitation and transfusion practices for this subset of casualties with exsanguinating hemorrhage. Military careproviders have found that massively bleeding patients may actually be harmed by standard approaches (Beekley A, MD, FACS, LTC, MC, US Army, personal communication, January 13, 2010). There is mounting evidence that these patients require an approach that begins treating all the physiologic derangements of massive blood loss as soon as possible after injury (Beekley A, MD, FACS, LTC, MC, US Army, personal communication, January 13, 2010). This realization has strongly influenced current damage control resuscitation practices, which are described in detail below.

> Military careproviders have found that massively bleeding patients may be harmed by standard approaches to resuscitation. Such casualties require an approach that immediately treats all physiologic derangements associated with massive blood loss.

Massive Blood Transfusion

Massive blood transfusion requires extensive blood banking resources and is associated with high mortality.[89,90,91,92,93,94] The most frequently used definition of massive transfusion is replacement of a patient's entire blood volume or 10 or more units of blood transfused in 24 hours.[95,96] Massive blood transfusion is infrequent in civilian trauma, occurring in only 2 to 13 percent of trauma admissions.[93,97] Due to a higher rate of penetrating injury in combat casualties, massive transfusion occurred in approximately 8 percent of OIF admissions and in as many as 16 percent during the Vietnam War.[98,99]

Resuscitation of exsanguinating patients is a challenging problem that is exacerbated when clear massive transfusion protocols have not been developed.[100] Although many institutions have massive transfusion protocols in place, adherence to such guidelines requires strong collaboration and effective communication between providers in the emergency department, operating room, ICU, and blood bank.[101] A study by Dente et al. demonstrated that the institution of a massive transfusion protocol in a civilian trauma center reduced early coagulopathy and decreased mortality in blunt trauma patients.[102]

Red Blood Cells

Patients requiring blood can safely receive uncrossmatched Type O blood until type-specific products are available.[103,104,105] Although type-specific uncrossmatched blood has also been used successfully for massive transfusion, acute hemolytic reactions have been reported.[106,107,108]

Fresh Frozen Plasma

Fresh frozen plasma (FFP) has been recognized as an important component in preventing and treating coagulopathy in trauma.[14,109,110,111] A donor unit of whole blood (approximately 450 milliliters) is separated into several components, with the plasma comprising approximately 250 milliliters (ml) of the liquid portion of blood containing water, electrolytes, and proteins (and lacking red blood cells, leukocytes, and platelets) (Fig. 12). The plasma proteins include the major clotting factors and intrinsic anticoagulants. In addition to the coagulation factors, the plasma found in one unit of whole blood also contains approximately 500 milligrams (mg) of fibrinogen (approximately equal to the amount of fibrinogen found in two units of cryoprecipitate).[112] While most clotting factors are stable at normal concentrations in plasma, some factors including factor V and factor VIII, termed labile factors, degrade over time; this degradation accelerates while plasma is stored in the liquid state (hence, why plasma is stored in a frozen state).

Transfusion of fixed ratios of FFP to RBCs has been proposed as a strategy to manage coagulopathy, particularly with rapid exsanguination and absent lab testing. Data from combat casualties in OIF support the use of plasma transfusion, showing a 65 percent mortality for patients who receive less than one unit of FFP for every four units of RBCs compared to a 19 percent mortality with more than one unit of FFP for every two units of RBCs.[113] While the optimal FFP to RBC ratio is unknown, mathematical models for FFP transfusion have been developed that support clinical data, suggesting that a ratio of 2:3 to as high as 1:1 (units of FFP to RBC) would be appropriate.[114,115]
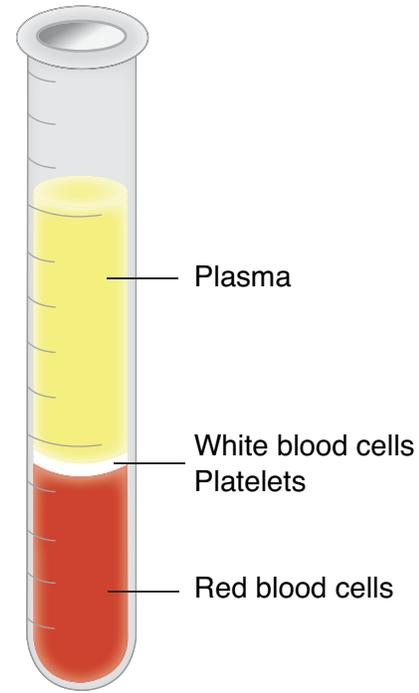
Plasma

White blood cells
Platelets

Red blood cells

Figure 12. *Blood may be transfused as whole blood, or separated into its components via centrifugation.*

> The optimal FFP to RBC ratio is unknown. Both mathematical models and clinical data for FFP transfusion favor a ratio of 2:3 to as high as 1:1 (units of FFP to RBC).

It has been suggested that FFP should be transfused early in the resuscitation to prevent dilutional coagulopathy.[73,94,96] Unfortunately, thawing of FFP is time-consuming, and patients often receive more blood or crystalloids in place of FFP, further exacerbating coagulopathy. Once patients have been stabilized, fixed FFP to RBC ratios are less critical, and standard transfusion strategies for plasma may be more appropriate. Standard transfusion criteria for plasma products include an INR greater than or equal to 1.5 or prolonged R-time on thromboelastography in the presence of active bleeding, or in a patient at high-risk for recurrent bleeding.[75]

All studies to date examining plasma, as well as other products including whole blood, platelets, and fibrinogen, have been retrospective and cannot be used to make definitive conclusions about the best care for trauma casualties. With retrospective analyses, there is the influence of survival bias that excludes patients dying quickly before being able to receive products such as plasma or platelets. It remains possible that patients received products such as plasma or platelets because they survived as opposed to surviving because

they received the products.[116] A recent study by Watson et al. even linked administration of FFP with a higher subsequent risk of developing multiple organ failure and acute respiratory distress syndrome.[117] Further prospective study evaluating the use of blood products in fixed ratios is warranted prior to drawing any definitive conclusions.

Platelets

Retrospective civilian data have supported the use of platelets in patients requiring massive transfusion.[92,109,118] Apheresis platelets (aPLT) have been available in Iraq since November 2004. Apheresis is the process of removing select components such as platelets from blood and returning remaining components to the blood. Emerging data from OIF have shown an improved survival at 24 hours in patients receiving a high platelet ratio greater than or equal to 1:8 apheresis platelet unit per stored red blood cell unit (aPLT to RBC) as compared to patients receiving a medium ratio (less than 1:8 to 1:16 aPLT to RBC), and patients receiving the lowest ratio of platelets (less than 1:16 aPLT to RBC) (24-hour survival 95 percent, 87 percent, and 64 percent, respectively).[116] The survival benefit for the high and medium ratio groups persisted at 30 days as compared to the lowest ratio group (75 percent and 60 percent versus 43 percent). On multivariate regression, the aPLT to RBC ratio was independently associated with improved survival at 24 hours and at 30 days.[116] A single unit of apheresis platelets is approximately equal to six units of pooled platelets. To simplify massive transfusion protocol strategies, the current Joint Theater Trauma System guidelines recommend transfusion of 1:1:1 pooled platelets to FFP to RBC (or 1:6:6 apheresis platelets to FFP to RBC) for patients requiring or anticipated to require massive transfusion.

As with plasma, once patients have been stabilized, platelet transfusion in a fixed ratio with RBCs may be less critical, and standard transfusion strategies for platelets may be more appropriate. The commonly recommended platelet transfusion threshold is a platelet count below 50,000/μL in patients with active bleeding.[119] In cases of high-energy multisystem trauma or central nervous system bleeding frequently seen in combat casualties, a higher platelet transfusion threshold of 100,000/μL has been recommended.[120]

Fibrinogen

Fibrinogen depletion develops earlier than other coagulation factor deficiencies.[121] Fibrinogen ratios examined in OIF casualties, and fibrinogen to RBC ratios of less than 0.2 g fibrinogen per RBC unit were associated with a higher mortality.[122] Given that there are 0.4 g of fibrinogen in one unit of FFP, administration of FFP in appropriate ratios (1:2 to 1:1) exceeds this fibrinogen ratio. Most deployed medical units do not have the capability to check fibrinogen in the laboratory, although thromboelastography is available at some Level III CSHs and can detect hypofibrinoginemia. Clot strength, as measured by the maximum amplitude on thromboelastography, is influenced by both platelet function and fibrinogen concentration. In cases where the platelet count is adequate, a decreased maximum amplitude would indicate hypofibrinoginemia.[123]

Fresh Whole Blood

Fresh whole blood (FWB), defined as blood collected and maintained at 22°C for a maximum of 24 hours, is rarely used in civilian practice.[124] However, the military has relied upon the use of FWB in circumstances when stored blood products are unavailable.[125] As FWB contains red blood cells, plasma, and platelets in physiologic ratios and contains less total preservative solution – compared to a mixture of separate RBC, FFP, and platelet components – some have advocated that FWB is a superior resuscitation product.[126,127] In a

retrospective study of 354 patients with traumatic hemorrhagic shock receiving blood transfusion, both 24-hour and 30-day survival were higher in the FWB cohort as compared to a component therapy group.[128] An increased amount (825 ml) of additives and anticoagulants were administered to the component therapy as compared to the FWB group. More recent data on combat casualties has tempered this conclusion, showing equivalence of 24-hour and 30-day survival between massively transfused patients receiving apheresis platelets compared to those receiving FWB.[276]

> In patients with hemorrhagic shock, when standard blood components such as apheresis platelets or plasma are unavailable, FWB is a lifesaving alternative.

Massive Transfusion-Associated Complications

Electrolyte Disorders

Hyperkalemia is a common complication with rapid or large-volume transfusion of red blood cells. Increased levels of extracellular potassium develop during the storage of red blood cells with concentrations averaging 12 milliequivalents (mEq) per liter at seven days and increasing to 32 mEq per liter after 21 days of storage.[129] Massive transfusion of senescent red blood cells could produce ventricular arrhythmia and cardiac standstill.[130,131] Some authors have theorized that effects of hyperkalemia may be mitigated by infusing blood into lines farther away from the right atrium to permit greater mixture of blood before arrival to the heart.[125] Fresher blood may also be requested from the blood bank or may be considered as an institutional policy for massively transfused patients. Once massive transfusion-associated hyperkalemia develops, it is treated in a conventional manner based on the clinical scenario (e.g., intravenous calcium, dialysis, dextrose and insulin infusion, bicarbonate, and diuretics).

> Hyperkalemia, due to extracellular potassium build-up in stored red blood cells, and hypocalemia, due to the binding of ionized calcium by citrate, may cause cardiovascular toxicity following large-volume transfusions.

Massive transfusion-associated hypocalcemia results from the presence of citrate as an anticoagulant in blood products (and subsequent citrate binding of serum ionized calcium), particularly in those with high plasma content such as FFP and platelets.[132,133] Citrate metabolism may be dramatically impaired in patients with hypoperfusion states, hypothermia, and advanced liver disease. This can produce citrate toxicity with resultant hypocalcemic tetany, prolonged QT interval on electrocardiogram, decreased myocardial contractility, hypotension, narrowed pulse pressure, and elevated end-diastolic left ventricular and central venous pressures.[134] If hypocalcemia is anticipated based on the clinical features, electrocardiographic changes, or ionized calcium levels, it may be managed with intravenous calcium chloride or calcium gluconate.

Massive Transfusion-Associated Coagulopathy

Coagulopathy is frequently present on admission in severely injured patients, particularly with brain or penetrating trauma injuries, and is associated with increased mortality.[17,52,94,135,136,137]Coagulopathy leads to further hemorrhage and worsening physiologic derangements, in turn prompting additional fluid

resuscitation and transfusion that can exacerbate coagulopathy, particularly if not appropriately managed, leading to the "bloody vicious cycle."[11]

Absent laboratory testing, clinical factors such as severe injury, shock, and hypothermia can predict coagulopathic bleeding.[118] Coagulopathy may be clinically recognized as abnormal microvascular bleeding of uninjured mucosal or serosal surfaces, or by prolonged bleeding at sites of vascular access and wound tissue surfaces following control of vascular bleeding.[138] At times, coagulopathy may not be recognized immediately and can be further obscured by standard clinical laboratory tests that fail to reflect clinically observed (in vivo) coagulopathy.[139] The laboratory values that are most frequently abnormal in the setting of coagulopathy are the PT time (97 percent), platelet count (72 percent), and aPTT (70 percent).[140] Notably, abnormal coagulation tests have been associated with increased mortality.[141] Thromboelastography, while less widely available at medical centers, is a method of measuring whole blood coagulation and has been proposed as a more accurate marker of coagulopathy and predictor of transfusion requirements than standard coagulation tests (Fig. 13).[75,142] More studies are needed to better define the potential role of thromboelastography as a diagnostic test and its ability to guide subsequent transfusion practices.[128]

Normal

Anticoagulants/Hemophilia

Platelet Blockers

Fibrinolysis
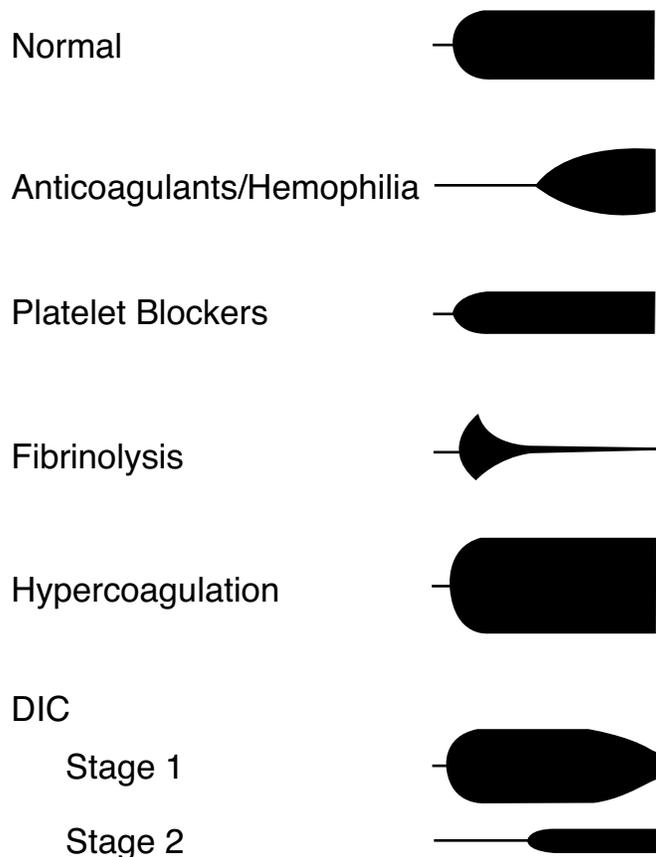
Hypercoagulation

DIC
Stage 1
Stage 2

Figure 13. *Illustration of thromboelastography patterns. This method of measuring whole blood coagulation has been proposed as a more accurate marker of coagulopathy and predictor of transfusion requirements than standard coagulation tests.*

Factors contributing to coagulopathy in patients undergoing massive transfusion include systemic acidosis, hypothermia, and consumptive and dilutional coagulopathy. Acidemia, largely due to lactate production by hypoperfused tissues utilizing anaerobic metabolism, can develop during hemorrhagic shock.[143,144,145] Acidosis may both exacerbate and cause coagulopathy.[118,146,147] Clotting factors and platelet aggregation are impaired by acidosis.[148,149] There is also evidence of natural anticoagulant activation through protein C and enhanced fibrinolysis through increased tissue plasminogen activator release and plasminogen-activator inhibitor-type 1 (PAI-1) depletion in shock and acidosis.[150,151]

Coagulopathy may be present on admission in severely injured patients and is associated with increased mortality. Factors contributing to coagulopathy in patients undergoing massive transfusion include systemic acidosis, hypothermia, and consumptive and dilutional coagulopathy. Though standard coagulation tests (INR, aPTT, and platelets) are relied upon, thromboelastography may be a more accurate marker of coagulopathy and predictor of transfusion requirements.

Hypothermia impairs the coagulation system in multiple ways.[36,39,152,153,154] Hypothermia has a modest effect on coagulation factor activity with a reduction of 10 percent of clotting factor activity for each 1°C decrease in temperature.[13] It also results in a marked effect on platelet function.[13,155,156] Platelet dysfunction develops due to defects in platelet activation, adhesion, and aggregation. Normalization of body temperature has been found to reverse inhibition of thrombin generation on platelets.[157,158,159]

Consumption of factors with disseminated intravascular coagulation (DIC) has been noted in early trauma, particularly in association with extensive endothelial injury, massive soft-tissue damage, fat embolization from long-bone fractures, and brain injury.[160,161] In addition to consumption of clotting factors, there is dysregulation of coagulation through consumption of antithrombin III, acquired platelet defects, and through increased fibrinolysis from increased tissue plasminogen activator and decreased α-2 antiplasmin.[162,163,164,165,166,167]

Dilutional coagulopathy develops during DCR as a consequence of the replacement of lost whole blood with coagulation factor-poor and platelet-poor fluids like crystalloids, colloids, and stored packed red blood cells.[126,168] In addition to coagulation factor and platelet deficiencies, a lowered hematocrit may further contribute to coagulopathy as erythrocytes marginalize platelets toward the capillary wall and endothelium.[169] Local platelet concentrations along the endothelium are nearly seven times higher than the average blood concentration due to this effect.[170] Studies have shown that anemia has been correlated with increased bleeding times that are reversible with RBC transfusion.[171,172] While clotting factors and platelets can be transfused during DCR, preservatives in these solutions of stored blood products may further worsen the dilutional coagulopathy.[126]

Damage Control Resuscitation Adjunctive Measures

Hypotensive Resuscitation

The practice of hypotensive resuscitation (permissive hypotension) has been traced back to Walter Cannon, who in 1918 proposed hypotension as a method for reducing uncontrolled internal hemorrhage.[173] Hypotensive resuscitation has been described as a method to improve patient outcomes by simultaneously limiting active hemorrhage and dilutional coagulopathy by tolerating lower than normal blood pressures (e.g., systolic pressure of less than 90 mm Hg) in trauma patients.[12] The combined effect of the natural coagulation cascade, hypotension, and vessel spasm is thought to temporarily arrest traumatic hemorrhage and serves as the underlying foundation for hypotensive resuscitation.[4,12,174,175,176,177] The direct effects of hypotensive resuscitation, or the failure to employ hypotensive resuscitation, are most readily apparent in traumatic amputation patients (Fig. 14). These patients often arrive without apparent bleeding from traumatically amputated limbs, only to have rapid arterial bleeding resume once resuscitation begins and hypotension is corrected to normal systolic pressures. This bleeding can sometimes overwhelm tourniquet control.[178] This rebleeding phenomenon was well-known and previously described by World War I and II era surgeons.[179]

Figure 14. *Overly aggressive fluid resuscitation of patients with traumatically amputated limbs may cause nonbleeding wounds to hemorrhage profusely. Image courtesy of the Borden Institute, Office of The Surgeon General, Washington, DC.*

Current military doctrine and training emphasize minimizing fluid and blood product delivery in prehospital settings for combat casualties who have a palpable radial pulse and normal mental status. The combined effect of the natural coagulation cascade, hypotension, and vessel spasm is thought to temporarily arrest traumatic hemorrhage and serves as the underlying foundation for hypotensive resuscitation. Such strategies are inappropriate with central nervous system injury or when cardiovascular collapse is imminent.

Several terms have been used to describe the strategy of tolerating relative hypotension in trauma victims prior to surgical hemorrhage control. These terms include hypotensive resuscitation, deliberate hypotension, and permissive hypotension. Although mixed results have been noted in studies, both animal and human clinical trials have supported the concept.[12,176,180,181,182,183,184,185,186,187,188] Current military doctrine and training emphasize minimizing fluid and blood product delivery in prehospital settings for combat casualties who have a palpable radial pulse and normal mental status.[189,190] This approach is also employed in the trauma bays with Forward Surgical Teams and CSHs to prevent unnecessary blood loss before surgical control is achieved.[190]

The challenge to providers using hypotensive resuscitation as part of their strategy is recognizing when to withhold additional fluid, but also knowing when such strategies are inappropriate, such as with central nervous system injury or when cardiovascular collapse is imminent.[191] Tissue ischemia followed by reperfusion is associated with biochemical and cellular changes resulting in complement activation and inflammatory responses.[192,193] These inflammatory responses are responsible for the development of acute lung injury and multiple organ failure, and are potentially exacerbated by the choice of resuscitation fluid.[194,195] The understanding of these processes is incomplete and an area of active research.

Patients with active hemorrhage may deteriorate quickly, and currently there are few data available to guide the hypotensive resuscitation strategy. As a general recommendation, patients are permitted to remain mildly hypotensive in two clinical circumstances. The first is the patient who is being rapidly transported to an operating room with the anticipation that surgical control of hemorrhage will be obtained quickly. Volume administration prior to hemorrhage control has the potential to raise the SBP sufficiently to overcome the natural hemostatic mechanisms. The second circumstance is for the patient with noncompressible hemorrhage who is a great distance from an operating room, either geographically or temporally. These patients may reach a temporary stable state where natural hemostatic mechanisms have slowed or stopped ongoing hemorrhage. Large volumes may overwhelm this natural hemostasis and cause exsanguination during transport. In both cases, the goal should be transfer to an operating room at the earliest possible time.

Optimal Use of Crystalloid and Colloid Solutions

Crystalloids and colloids greatly intensify dilutional effects if given in significant quantities (greater than 20 ml per kilogram). In addition to dilutional effects, colloids such as hydroxyethyl starch (HES) are also known to increase coagulopathy by impairing von Willebrand factor activity in plasma.[196,197] Moreover, a preventable cause of iatrogenic acidemia involves the choice of resuscitation fluid. The two most commonly used isotonic crystalloid solutions in emergency departments and prehospital settings are lactated Ringer's solution and normal saline. Both of these fluids possess pH ranges as low as 4.5 for normal saline (NS) and 6.0 for lactated Ringer's (LR) solution.

> Crystalloids and colloids greatly intensify hemodilutional effects if given in significant quantities (greater than 20 ml per kilogram). The low pH values of normal saline and lactated Ringer's solution contribute to iatrogenic acidemia when administered in large volumes.

In a fairly extensive review of animal research, case reports, case series, and clinical studies, Ho and colleagues demonstrated that use of large amounts of normal saline in trauma patients with shock contributes to metabolic acidosis, which also can significantly worsen coagulopathy.[198] This effect was not demonstrated with lactated Ringer's solution. Several other recent animal studies have demonstrated superiority of lactated Ringer's solution over normal saline as a resuscitation fluid in hemorrhagic shock.[199,200,201] Nevertheless, the choice of lactated Ringer's solution as a resuscitation fluid, particularly for severely injured patients undergoing damage control surgery and massive transfusion, has other drawbacks. Lactated Ringer's solution in large volumes provides little or no direct contribution to improve coagulation or oxygen-carrying capacity, relative to early use of blood products. More recently, lactated Ringer's solution has also been found to dramatically activate the immune system and potentially contribute to secondary cellular injury.[190,202,203,204,205] Use of this fluid may be detrimental in patients with uncontrolled hemorrhage.[176,180,181]

Vasoactive Agents

Exogenous catecholamines and other vasopressor agents (e.g., vasopressin) are used frequently as adjuncts to the resuscitation of patients with severe hemorrhagic shock. Although previous data on the employment of vasopressors in hemorrhagic shock are mixed, recent animal studies reveal potentially favorable results with the use of low-dose vasopressin in resuscitation after brain injury or hemorrhage and blunt pulmonary contusion or hemorrhage.[206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221] Other investigators have shown that vasopressin becomes deficient in advanced stages of hemorrhagic and vasodilatory shock and hence is an appropriate target for replacement.[222] A recent review article by Cohn suggests that low-dose vasopressin in severe hemorrhagic shock can lower resuscitation volumes and potentially improve morbidity and mortality.[223] Overall, the multiple publications analyzing the effects of low-dose vasopressin in various clinical settings have resulted in conflicting results.[217,218,219,224,225,226,227,228,229,230,231] Further well-designed clinical trials in trauma patients are necessary to better define the role of vasoactive agents (e.g., vasopressin) as adjuncts to resuscitation.

> While exogenous catecholamines and other vasopressor agents are frequently used during resuscitation of patients with severe hemorrhagic shock, further studies are necessary to establish their efficacy.

Nonsurgical Hemostatic Agents

Topical Sealants

Topical hemostatic sealants are used as adjuncts for local hemostasis in cases where conventional measures for bleeding control fail. Agents such as FLOSEAL™, GELFOAM®, and SURGICEL® are useful adjuncts to standard hemorrhage control techniques in patients undergoing cardiac, vascular, and spinal surgery.[232,233,234]

Recombinant Factor VIIa

While recombinant factor VIIa (rFVIIa) is currently only approved for the management of bleeding in patients with congenital Factor VII deficiency and hemophilia A or B with inhibitors, this agent has been extensively used off-label in trauma. Further interest was spurred following a series of experimental animal liver trauma studies that showed prolongations in survival and decreased blood loss with its use.[235,236,237,238,239] These studies coincided with a number of subsequent case reports and case series of rFVIIa use in trauma and uncontrolled hemorrhage suggesting decreased blood loss or decreased transfusion requirements for patients.[98,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260]

> As of 2009, there is no evidence of improved major clinical outcomes (e.g., decreased mortality) as a direct result of using rFVIIa in the management of trauma patients.

The only randomized trial of rFVIIa in trauma patients (published in 2005) randomized 301 patients with blunt or penetrating injuries to receive placebo or rFVIIa after the eighth unit of blood.[261] This trial showed a reduction of 2.6 units of RBC transfusions for the blunt trauma subgroup and a similar though non-significant trend in the penetrating injury subgroup receiving factor rVIIA. While trends toward reductions in mortality and critical complications were seen, no statistically significant results were documented.[261] The CONTROL study, a randomized double-blind trial whose purpose was to evaluate the safety and effectiveness of rFVIIa in severely injured trauma patients, was discontinued at Phase III because a preplanned futility analysis predicted a very low likelihood of reaching a successful outcome on the primary

efficacy endpoints.[262] As of 2010, there is no evidence of improved major clinical outcomes (e.g., decreased mortality) as a direct result of using rFVIIa in the management of trauma patients.

The potential for thromboembolic complications associated with rFVIIa has received considerable attention. Meta-analyses of randomized, controlled trials have shown mixed results while multiple studies have suggested that thromboemboli are an apparent complication.[263,264,265,266,267,268,269]

Antifibrinolytics

As hyperfibrinolysis is a contributor to the coagulopathy of trauma, antifibrinolytics have the potential to reduce blood loss and improve outcomes in traumatic bleeding. Antifibrinolytic agents have been noted to reduce blood loss in patients with both normal and exaggerated fibrinolytic responses to surgery.[270] The most extensively evaluated agents are aprotinin, epsilon aminocaproic acid, and tranexamic acid. The Food and Drug Administration suspended marketing of aprotinin in November 2007 due to reports of increased mortality in coronary bypass surgery.[271] While aminocaproic acid is approved by the FDA for enhancing hemostasis in states of hyperfibrinolysis, and tranexamic acid is approved for hemophilia patients undergoing tooth extraction, a Cochrane Review of antifibrinolytic drugs in acute traumatic injury revealed no studies of sufficient quality to assess the benefits in this population.[272,273,274] There is currently a major ongoing international trial, CRASH-2: Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (NCT00375258), to evaluate the use of tranexamic acid compared to placebo in trauma patients.[275] Until these results are available, there is little role for the prophylactic or empiric use of antifibrinolytics in acute trauma.

Conclusions

The resuscitation of severely injured trauma patients will continue to remain a complex and multifaceted problem. The recent large numbers of combat casualties requiring massive transfusion, an unfortunate by product of modern war, has enabled both the military and civilian trauma communities to formulate an evolving DCR strategy. Ongoing and future research are needed to further refine and validate: (1) novel prehospital therapies for the treatment of noncompressible hemorrhage; (2) technologies to rapidly assess the physiologic status of injured patients; (3) methods to select patients for damage control approaches; (4) the optimal content and proper sequence of administration of resuscitation products; and (5) novel approaches to managing patients at or near the limits of physiologic reserve.

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