# Damage control resuscitation: A sensible approach to the exsanguinating surgical patient

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Background: The current wars in Iraq and Afghanistan have resulted in the highest rates of combat casualties experienced by the U.S. military since the Vietnam conflict. These casualties suffer wounds that have no common civilian equivalent and more frequently require massive transfusion (greater than 10 units of packed red blood cells [PRBCs] in less than 24 hrs) than civilian injured.

*Discussion:* Military surgeons have found that traditional approaches to resuscitation, particularly in terms of the ratio of blood products to each other and the timing of these products, often fail to effectively treat the coagulopathy that is present on arrival in these casualties. This observation has been concurrently noted in the civilian trauma literature. These experiences have ignited interest in an alternative approach to the resuscitation of these most grievously injured patients. This approach includes the use of permissive hypotension; the prevention and aggressive

treatment of hypothermia with both passive and active warming measures; the temporization of acidosis with use of exogenous buffer agents; the immediate use of thawed plasma in ratios approaching 1:1 with PRBCs; the early use of platelets, often given well before 10 units of PRBCs have been transfused; the early use of recombinant Factor VIIa; and, in military settings, the use of fresh whole blood as a primary resuscitation fluid. This strategy has been called "damage control resuscitation" to emphasize its pairing with damage control surgical techniques.

*Summary:* Review of the published support for this strategy reveals that additional trials are needed to study and optimize these techniques. (Crit Care Med 2008; 36[Suppl.]:S267–S274)

KEY WORDS: damage control resuscitation; massive transfusion; exsanguination; fresh thawed plasma; fresh whole blood; hemostatic resuscitation; hypotensive resuscitation; permissive hypotension; coagulopathy; lethal triad

he term "resuscitation" has evolved in modern medical lexicon to encompass the entire spectrum of care delivered to a surgical patient in physiological distress or shock. Far from just the amount and type of fluids used, this spectrum of care includes a standard and finite set of invasive interventions during the initial primary survey of the injured patient, the diagnostic means used to discover sources of injury and shock, the advanced surgical interventions used to treat these injuries, the reversal of hypothermia, the correction of acidosis, and the replacement of intravascular volume, oxygencarrying capacity, and coagulation factors. However, for the purposes of this article, "resuscitation" refers to the non-

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surgical strategies used to prevent or reverse anemia, coagulopathy, acidosis, and hypothermia in the presentation and initial 24 to 48 hrs of care of the severely injured patient.

With the advent of modern blood centrifuge, preservation, and banking, the major logistic hurdle involved in having rapidly available blood products on hand for injured patients was largely overcome. At roughly the same time, it was discovered that relatively simple isotonic crystalloid solutions could provide initial and, in many cases, adequate resuscitation for most injured casualties. The administration of isotonic crystalloid solutions to acutely injured patients has become a standard practice that remains in the Advanced Trauma Life Support courses taught today (1). Until recently, massive transfusion guidelines for the ratio of various products administered were based on the assumption that the coagulopathy encountered in severely injured patients was primarily from dilution of blood clotting constituents and did not occur until at least one blood volume had been transfused (2).

The notions that substantial volumes of isotonic crystalloid solutions are acceptable for severely injured patients and

that coagulopathy is primarily a byproduct of resuscitation have recently been challenged (3). Several recent articles from major civilian and military trauma centers have demonstrated that severely injured casualties have a significant coagulopathy on presentation (4-6). Not surprisingly, these severely injured patients are also the ones most likely to experience hypothermia and acidosis. Adherence to the traditional practice of administering isotonic crystalloids followed by packed red blood cells (PRBCs) until a either a predetermined threshold of PRBCs is reached or until fresh frozen plasma can be thawed results in a worsening of all three aspects of the "lethal triad."

In many of the classic papers that describe reversing the "lethal triad" of hypothermia, acidosis, and coagulopathy with "damage control" approaches, the authors break down the various aspects of the damage control process into sequences or steps for simplicity (7–9). An unfortunate byproduct of describing the damage control sequence in phases is the potential inference that correction of the hypothermia, acidosis, and coagulopathy is the "secondary resuscitation," which does not begin in earnest until the patient reaches an intensive care unit.

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The emphasis in many of these papers is on the very concept of delaying definitive surgical treatment until the patient's hypothermia, acidosis, and coagulopathy are treated and on the surgical techniques used to perform an abbreviated operation. The intraoperative resuscitation strategies described often featured initial resuscitation with crystalloid, transition to PRBCs for continued evidence of shock, and addition of plasma and platelets into the resuscitation strategy only after a certain threshold of PRBC numbers (for example, 8–10) had been reached (8).

That this resuscitation strategy fails to treat and in fact worsens the hypothermia, acidosis, and coagulopathy that are associated with severe trauma has been recently noted by several authors, including surgeons deployed in the global war on terrorism (10, 11). An alternative strategy, aptly named "damage control resuscitation" to emphasize its pairing with damage control surgical techniques, is described and is currently in use in Operations Iragi and Enduring Freedom. This strategy includes the tolerance of moderate hypotension (systolic blood pressure approximately 90 mm Hg); the trauma system-wide emphasis on the recognition and prevention of hypothermia; the temporization of acidosis (or at least prevention of worsening acidosis); and the emphasis on immediate correction of coagulopathy as the most treatable arm of the "lethal triad." The treatment of coagulopathy features appropriate choices of resuscitation fluids; the amounts and ratio of these products to one another; the timing of the delivery of these products; and the use of adjuncts to resuscitation (for example, recombinant Factor VIIa). Clearly, for this resuscitation strategy to be successful, it must be married to the treatment of immediately life-threatening conditions (for example, tension pneumothorax) and the rapid surgical control of hemorrhage.

The majority (>90%) of trauma patients treated in both civilian and military settings do not require damage control surgical techniques or massive transfusion (defined as >10 units PRBCs in 24 hrs for this article) (12). Although it has been demonstrated that up to 28% of these patients may have an abnormal ProTime on arrival (5), more recent data suggest that thromboelastography may be superior to standard assays (such as ProTime and partial thromboplastin time) in detecting a hypercoagulable state early after injury in less severely injured patients (13). Hence, managing hypercoagulability may be more critical in the majority of less severely injured trauma patients. The need for massive transfusion is relatively rare, occurring in only 1% to 2% of civilian trauma patients (14), but up to 7% of patients in current military settings (11). However, these patients are the most at risk for early death from hemorrhage and stand to benefit from alternative strategy that begins to treat their physiological derangements as soon as they arrive (and preferably before they arrive).

## **Permissive Hypotension**

The concept that the combination of the patient's natural coagulation cascade, hypotension, and vessel spasm will temporarily arrest traumatic hemorrhage is perhaps no better illustrated than in the combat casualty with proximal limb amputations from an explosion. 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 will sometimes overwhelm tourniquet control (15). This phenomenon was well known and previously described by World War I and II era surgeons (16). Several terms have been coined to describe the strategy of allowing hypotension in trauma victims before the establishment of surgical hemorrhage control. These terms include hypotensive resuscitation, deliberate hypotension, and permissive hypotension; undoubtedly there are others. Both animal and human clinical studies have also supported this concept, although mixed results have been noted in clinical studies (17-28). Nevertheless, current military doctrine and training emphasize minimizing fluid and blood product delivery in the prehospital setting in combat casualties who have a palpable radial pulse and have normal mental status (29, 30). This approach is also used in the trauma bays at forward surgical teams and combat support hospitals to prevent unnecessary blood loss before surgical control is obtained.

## Hypothermia

The dramatic and negative association that hypothermia has with the survival of severely injured trauma patients is well

described. Severe trauma-related hypothermia (temperature  $<32^{\circ}$ C) has been associated with 100% mortality (31). The effect of hypothermia on the coagulation system is multifactorial (32, 33). Moderate hypothermia (32°C to 34°C) directly reduces coagulation factor activity approximately 10% for each degree Celsius decrease in temperature while markedly affecting platelet function (34-36). Severely injured trauma patients with hemorrhagic shock typically have uncoupling of normal metabolic pathways, resulting in the loss of homeothermic ability. This loss of thermoregulation can be exacerbated in the prehospital setting by environmental factors, prolonged extrication or scene time, intoxication, and convective heat losses (for example, open helicopter door during flight). Both civilian and military trauma centers have linked the presence of hypothermia on arrival with increased mortality (37–39).

Hypothermia in combat casualties was identified as a theaterwide trauma system problem in Operation Iragi Freedom (40, Several measures were subsequently put in place system-wide to prevent hypothermia. First, 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 that require treatment, wrapping treated casualties in wool or solar blankets, and the use of inline fluid warmers such as the Thermal Angel (Estill Medical Technologies, Dallas, TX). Measures to prevent and treat hypothermia at the initial levels of surgical care (forward surgical teams and combat support hospitals) include the use of standardized heat-loss prevention kits (use of solar blankets, heated blankets, and body bag[s]), the use of warmed blood products and fluids, and the use of fluid warmers/rapid infusers (for example, the Thermal Angel [Estill Medical Technologies, Inc., Dallas, TX] and the Belmont Rapid Infuser [Belmont Instrument Corporation, Billerica, MA]). Since institution of standardized hypothermia prevention measures, the rate of patients arriving to the combat support hospitals with hypothermia has dropped from 7% to less than 1% (41).

Hence, severe hypothermia has become a relative rarity in Operation Iraqi Freedom. The system measures in place allow prevention of additional heat loss in prehospital settings and prevention and treatment of hypothermia are the standard care a casualty receives on arrival to the hospital. Aside from the standardized use of maximum warming settings on rapid infusers, the need for active rewarming measures such as continuous arteriovenous rewarming (42, 43) or body cavity lavage of warmed fluids has been largely obviated. Cardiopulmonary bypass, used in extreme cases of hypothermia for controlled active rewarming, is not available in the combat support hospitals in Iraq or Afghanistan.

#### Acidosis

The contribution of acidosis to the "bloody vicious cycle" (44) is well known if not entirely or clearly understood (45). In vitro studies have demonstrated substantially reduced clot formation rate as detected by thromboelastography in normal blood brought to a pH of 7 (46), and platelets incubated in a low pH (5.5) form spheres devoid of aggregating tendency, whereas at a higher pH (9.0) they form pseudopodia that increase aggregation properties (47). Martini et al. demonstrated that acidosis reduced fibrinogen concentration, platelet counts, and thrombin generation in an animal model (48, 49). Meng et al. demonstrated reduced rates of activated Factor X formation by activated Factor VII/tissue factor complex in an acidic (pH <7.4) environment (50). Multiple clinical studies have also linked varying degrees of acidosis with coagulopathy and poorer outcomes in trauma patients (6, 45, 51-53).

Effective reversal of acidosis can be challenging in the severely injured or still actively hemorrhaging trauma patient and is essentially dependent on rapid control of hemorrhage and restoring global tissue perfusion. Several end points of resuscitation have been identified as goals for therapy. These end points traditionally include serum lactate and base deficit (54, 55), which reflect global tissue perfusion. Newer technologies such as the use of near-infrared spectroscopy (56-60), skeletal muscle acid-base status (61), and more sophisticated measures of global acid-base status (62) have been proposed and are under study. The ability to restore these end points to normal ranges has been shown to have prognostic significance (54, 58). Several techniques to temporarily ameliorate the negative effects of acidosis on the coagulation system have been proposed such as the administration of exogenous bicarbonate or tris-hydroxymethyl aminomethane. These interventions have had mixed results in studies and alone appear insufficient in reversing acidosis-induced coagulopathy (63, 64).

Perhaps more important than interventions to directly reverse acidosis is avoiding interventions that worsen acidosis. One potentially preventable and easily correctable cause of acidosis is hypoventilation. A second preventable cause of iatrogenic acidosis involves the choice of resuscitation fluid. The two most commonly used isotonic crystalloid solutions in emergency rooms and prehospital settings are lactated Ringer's and normal saline. Both of these fluids are labeled with pH ranges as low as 4.5 for normal saline (NS) and 6.0 for lactated Ringer's (LR). 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 NS in trauma patients with shock contributes to metabolic acidosis (65), which as discussed can significantly worsen coagulopathy. This effect was not demonstrated with LR, although large volumes can also cause this effect. Several other recent animal studies have demonstrated superiority of LR over NS as a resuscitation fluid in hemorrhagic shock (66-68).

Nevertheless, the choice of LR as a resuscitation fluid, particularly for severely injured patients requiring damage control surgical approaches and massive transfusion, has other drawbacks. LR in large volumes provides little to no direct contribution to improved coagulation or oxygen-carrying capacity. Use of this fluid may be detrimental in patients with an uncontrolled surgical hemorrhage source (20-22, 24). LR has also recently been demonstrated to dramatically activate the immune system and potentially contribute to secondary cellular injury (69–73).

## Coagulopathy

As discussed, considerable attention has been given to reversing the effects of the hypothermia and acidosis in the "lethal triad." Unfortunately, the therapies available to directly reverse these problems (when they are severe) are either invasive or cumbersome, as is the case in hypothermia, or relatively lacking in efficacy, as is the case in acidosis. Hence, preventing worsening hypothermia and acidosis are the strategies of choice, and the ultimate correction of hypothermia and acidosis is generally linked to the overall resuscitation of the patient. The remaining member of the "lethal triad," coagulopathy, has also been demonstrated to be present on arrival in severely injured trauma patients (4-6, 10, 74). Unlike its counterparts, there are a number of effective therapies and products available to directly treat coagulopathy. The renewed interest in therapies for coagulopathy reflects a realization that of the three parts of the "lethal triad," coagulopathy is perhaps the most readily treatable; and until recently, standard massive transfusion practices have undertreated it (11, 75–77).

#### Fresh Whole Blood

The key question driving current resuscitation research is "what is the optimal resuscitation fluid for a severely injured trauma surgical patient?" The simplest and idealized answer to this question may be "give the patient back the fresh whole blood that he lost." The reality is much more complex, particularly because modern experience with fresh whole blood as a resuscitation fluid is relatively small, and in all cases, the fresh whole blood was given in conjunction with a number of other more commonly used stored blood components. Nevertheless, a review of the literature of fresh whole blood offers some perspectives. First, animal studies evaluating whole blood have demonstrated that whole blood restores myocardial function better than PRBCs administered after severe hemorrhage in dogs (78); and fresh whole blood is the best 24-hr hypotensive resuscitation fluid after severe hemorrhage in swine (79). Manno and colleagues demonstrated that use of blood less than 48 hrs old reduced blood loss and transfusion requirements in neonates undergoing cardiac surgery (80). Erber and colleagues published a small series suggesting a benefit of unrefrigerated whole blood in severely hemorrhaging surgical patients (81). More recently, the U.S. Army has accumulated a great deal of experience using fresh whole blood in combat casualties in Operations Iragi Freedom and Enduring Freedom (82). The safety of a fresh whole blood program using rapid screening assays for infectious diseases has been demonstrated (83). Although data directly evaluating the efficacy of fresh whole blood use versus component therapy have yet to be published, initial evaluation of the data and anecdotal reports of "unexpected

survivors" suggest there may be a survival benefit to the use of fresh whole blood in massive transfusion (12, 15). This analysis is ongoing, and additional prospective studies are required to answer this question (75, 84). More details on the emergence of fresh whole blood transfusions are addressed elsewhere in this supplement.

The dramatic experiences reported by physicians using fresh whole blood to treat combat casualties, although anecdotal, have refocused resuscitation research toward strategies to mimic the delivery of whole blood by adjusting ratios of standard blood components and using adjuncts such as recombinant Factor VIIa. Unfortunately, the sum of combining standard blood component therapy does not equal the whole of a unit of fresh whole blood. Analysis of a unit of fresh whole blood reveals it contains approximately 500 mL of warm blood with a hematocrit of 38% to 50%, a platelet count of 150,000 to 400, essentially full coagulation function, and 1500 mg of fibringen. Combining one unit of PRBCs. one unit of platelets, one unit of fresh frozen plasma, and a ten-pack of cryoprecipitate provides 660 mL of fluid with a hematocrit of 29%, platelet count of 87,000, coagulation activity of approximately 65%, and 750 mg of fibrinogen (12, 85).

Additional problems have been identified with component therapy. Increasing blood transfusion rates correlate with increasing mortality in both civilian and military trauma patients (14, 86). Injury severity alone does not account for this correlation. A growing body of trauma and critical care literature demonstrate the detrimental effects of red blood cell transfusion on patient survival. Degradation of stored red blood cells over time, termed "storage lesion" (87), has been implicated in decreased red blood cell aggregation (88), increased inflammatory mediators (89), decreased 2,3-DPG activity and splanchnic ischemia (90), pneumonia and other infections (91), multiple organ failure (92), and mortality (93, 94). Currently, the average age of transfused red blood cells in Operation Iragi Freedom is 33 days (83), indicating that substantial storage lesion is likely present in the blood being transfused into combat casualties. Hence, the military has developed strategies to minimize the amount of red blood cell transfusions that are necessary by aggressively treating coagulopathy on patient arrival and, in some cases, preferentially switching to fresh whole blood as a primary resuscitation modality rather than just a logistic necessity (12).

# **Blood Product Ratios**

The focus on providing the optimal resuscitation fluid has also dramatically altered the use of standard blood components. Busy trauma centers, including those in Iraq and Afghanistan, now routinely thaw Type AB or A fresh frozen plasma each morning (relabeled "fresh thawed plasma," this product has a shelflife of 4 to 5 days; most is used the day it is thawed). These products are delivered to the trauma bay and operating room in standard resuscitation packs for delivery early in a severely injured trauma patient's course (95). The optimal ratios of red blood cells to plasma and platelets has yet to be elucidated in prospective trials; nevertheless, retrospective data from Operation Iraqi Freedom demonstrate a survival benefit when plasma to red blood cell ratios approach 1:1 (96). A similar trend has been demonstrated in an unpublished study done at 16 major civilian trauma centers (John B. Holcomb, MD, COL, Commander, U.S. Army Institute of Surgical Research, personal communication, December 3, 2007). The early use of ratios of plasma to red blood cells of 2:3 or approaching 1:1 have also been suggested in other published studies (76, 97-99). Researchers are also exploring the use of freeze-dried plasma products or the use of purified protein concentrates that use variable amounts of factors. These products are potentially safer from an infectious disease perspective, target factor replacement without the additional volume, and are logistically appealing given their small size.

# **Recombinant Factor VIIa**

The use of recombinant Factor VIIa remains a topic of considerable debate, and large, multicenter, prospective trials are ongoing to elucidate both efficacy and safety issues. Factor VIIa's efficacy has considerable support in anecdotal and animal research (100-111). Boffard and colleagues' prospective trial demonstrated reduction of blood transfusions with administration of Factor VIIa in blunt trauma patients but no effect on mortality (112). There is still considerable debate about the appropriate timing of drug delivery, the selection of patients to re-

ceive the drug, and whether additional blood components can be delivered with the drug to enhance its effect (113, 114). The drug appears to be less effective in the setting of acidosis (50) but remains effective in all but the most severely hypothermic settings (115). Recent reports regarding a potential for increased thromboembolic events has sounded a note of caution on the medication's liberal use until randomized, prospective trials conclude (116, 117). The use of recombinant Factor VIIa in damage control resuscitation should take these factors into account. The risk of subsequent thromboembolic events must be balanced against the more acute threat of exsanguination. Identification of the appropriate patient population in whom to use the medication will require completion of ongoing randomized, prospective trials and perhaps additional studies.

# Prospective Identification of Patients Who Require Damage Control Resuscitation

Because less severely injured trauma patients may theoretically manifest hypercoagulability, identification of candidates for damage control resuscitative techniques must be based on rapidly obtainable clinical parameters. In combat settings, in which roughly 95% of casualties present with a penetrating trauma mechanism, we have found certain patterns of injury that reliably predict need for massive transfusion and damage control surgical and resuscitative techniques. These patterns tend to be obvious and include patients with multiple proximal amputations (particularly thighlevel), truncal hemorrhage combined with a proximal amputation, and abdominal evisceration with hypotension. Penetrating mechanism has been shown to be an independent predictor of need for massive transfusion in combat casualties (6).

Other measurable parameters that have been suggested as predictors of massive transfusion requirements include a base deficit less than 6 (51), an international normalized ratio 1.5 or greater (5, 6, 76), a systolic blood pressure less than 90 mm Hg in combat trauma patients and less than 110 mm Hg in civilian trauma patients (118–120), hemoglobin less than 11 (6), temperature less than 96°F or 35°C to 36°C (37, 39, 121), and a weak or absent radial pulse (122). Patients with any of these clinical parameters, certainly if they are in combination or otherwise match physical examination findings, should be considered for immediate transition from a "standard" resuscitation mode to a damage control resuscitation mode (86).

#### Summary

Employment of damage control resuscitation begins as soon as the patient is identified as being at risk for death from hemorrhage. The patient will require rapid transfer to an operating room for initiation of damage control surgical techniques and early administration of increased amounts of thawed plasma and red blood cells than traditionally taught. Some authors recommend ratios approaching 1:1 (although further investigation needs to be performed before definitive conclusions can be made); minimization of crystalloid infusion; activation of massive transfusion or exsanguination prevention guidelines, which feature automatic delivery of predefined transfusion "packs" containing plasma, red blood cells, platelets, and potentially cryoprecipitate; consideration for early administration of recombinant Factor VIIa; institution of hypothermia prevention and treatment; and potentially the use of tris-hydroxymethyl aminomethane or other agents to buffer severe acidosis if present (10, 11). Validated end points of resuscitation such as correction of lactate and/or base deficit should be used to guide resuscitation. The use of thromboelastography (currently used in some combat support hospitals in Iraq) can potentially identify specific deficits in the patient's clotting cascade and decrease unnecessary transfusion of products.

#### **Future Directions**

It should be noted that the majority of the current published data examining the damage control resuscitation strategy are Class II or III data (retrospective observational studies) and that current prospective studies are underway. Many unanswered questions remain regarding the optimal resuscitation strategy for severely injured trauma patients. What are the optimal ratios of plasma, PRBCs, platelets, and fibrinogen-containing products? When should Factor VIIa be given, and can the administration of Factor VIIa with other products enhance its efficacy? Is there a role for other hemostatic agents (for example, tranexamic acid)? It is critical that these questions be studied through well-designed, multiinstitutional, randomized, prospective trials. This is a challenge; the resuscitation of severely injured patients in modern civilian and military trauma centers involves a complex interaction of multiple providers performing simultaneous interventions in which team dynamics, communication, logistics, provider experience, trauma center volume, as well as individual patient factors impact on the ultimate outcomes.

Perhaps the ultimate frontier of resuscitation research, and the ultimate "damage control" approach, is suspended animation. A number of researchers are currently investigating suspended animation using profound hypothermia, hydrogen sulfide, and nitric oxide (123–144). Although years away, the suspended animation approach may eventually provide salvage to trauma patients who arrive to surgical care at the limits of physiological reserve. Currently, this set of patients may undergo emergency department thoracotomy with predictably dismal results.

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