World Journal of Surgery

Published Online: 30 March 2007

World J Surg (2007) 31: 1055–1064
DOI: 10.1007/s00268-006-0653-9

Coagulopathy: Its Pathophysiology and Treatment in the Injured Patient

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Abstract
Hemorrhage continues to be one of the leading causes of death following trauma. Trauma patients are susceptible to the early development of coagulopathy and the most severely injured patients are coagulopathic on hospital admission. Hypothermia, acidosis, and dilution from standard resuscitation can worsen the presenting coagulopathy and perpetuate bleeding. Early identification of coagulopathy is dependent on clinical awareness and point of care laboratory values. Routinely used laboratory coagulation parameters fail to adequately describe this state. Thrombelastography is a test that can be done at the bedside and uses whole blood to provide a functional evaluation of coagulation. Rapid diagnosis of coagulopathy, followed by prevention or correction of hypothermia and acidosis should be a priority during the initial evaluation and resuscitation. Judicious use of resuscitation fluids and early replacement of coagulation factors will help prevent iatrogenic hemodilution. This review covers the pathophysiology as well as the clinical and laboratory diagnosis of coagulopathy. Prevention and treatment strategies are discussed, including early transfusion of coagulation factors during massive transfusion and the use of recombinant factor VIIa. Damage control resuscitation is briefly discussed, and it involves the combination of hypotensive resuscitation and hemostatic resuscitation. Finally, a description of the use of fresh whole blood in the military setting is included. Its use has been proven to be safe and beneficial in this setting and warrants further investigation as an adjunct to the management of civilian trauma patients.

Trauma is an international endemic that threatens persons from all walks of life. In 2003 it was the leading cause of death in individuals aged 1–44 years, with the highest incidence in those 35–44 years of age.[1] Hemorrhage ranks second to central nervous system injuries in overall cause of death, accounting for 30%–40% of fatalities, and it is the leading cause of preventable deaths. The extent of hemorrhage depends on a combination of factors that include the degree of vascular disruption, blood pressure, volume resuscitation, and time between injury and definitive hemostasis. Hemorrhage is an acute problem that accounts for a significant portion of pre-hospital and hospital admission mortality within the first 48 h.[2–4] Patients who arrive in hemorrhagic shock can go on to develop an acquired coagulopathy that is associated with an increase in overall mortality.[5]

The development of systematic regionalized trauma systems have provided rapid transport from the scene of injury to trauma centers that can provide expeditious treatment and intervention for severe hemorrhage. Current advanced trauma life support (ATLS) guidelines state that blood loss should be replaced with a 3 to 1 ratio of isotonic crystalloid fluid. In addition to resuscitating trauma victims, it is important to minimize further bleeding

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Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01 MAY 2007	**N/A**	**-**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Coagulopathy: its pathophysiology and treatment in the injured patient	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
Tieu B. H., Holcomb J. B., Schreiber M. A.,	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT NUMBER
United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX 78234	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			
unclassified	**unclassified**	**unclassified**	**UU**	**11**	

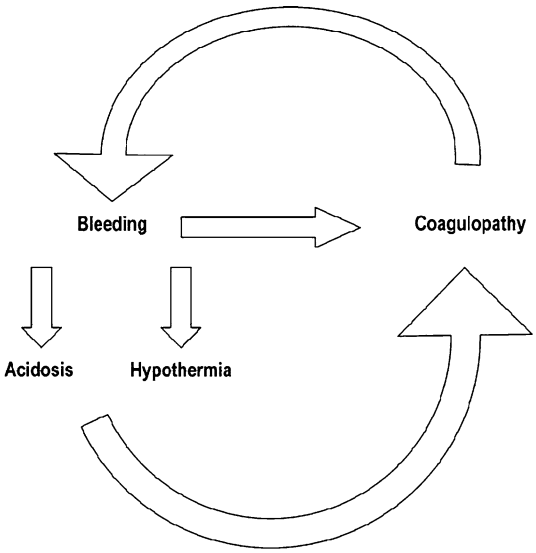

Figure 1. Depiction of lethal triad. Blood loss leads to acidosis and hypothermia resulting in coagulopathy that perpetuates further bleeding. Reprinted from Schreiber MA, Damage control surgery. Critical Care Clinics 20:101–118, 2004 with permission from Elsevier.

and prevent exacerbation of coagulopathy. Aggressive resuscitation with a goal to normalize vital signs can result in rebleeding, hypothermia, and dilution, which perpetuate coagulopathy and the ''lethal triad'' (Fig. 1).

In this review, we describe the pathophysiology of coagulopathy after trauma. We discuss its prevention and early treatment, including early transfusion of coagulation products during massive transfusion with packed red blood cells (pRBC), the use of recombinant Factor VIIa (rFVIIa), and limited resuscitation with crystalloids and colloids. A description of the current use of fresh whole blood (FWB) in the military setting is included.

HEMOSTASIS AFTER INJURY

Hemostasis is a complex process that limits blood loss following vascular injury. Four major physiologic events participate in this process: vasoconstriction, platelet plug formation, fibrin formation, and fibrinolysis. These events generally occur in the listed order but they are interdependent. In the absence of vascular injury, endothelial cells prevent thrombosis by secretion of nitric oxide, which prevents platelet activation, and tissue plasminogen activator, which breaks down fibrin. Endothelial cells also express heparan sulfate, a cofactor for antithrombin III and thrombomodulin that conforms thrombin to activate protein C.[6,7] Vascular injury results in endothelial cell activation and secretion of the procoagulant plasminogen activator inhibitor-1.

Extensive tissue injury and further disruption of endothelial surfaces exposes collagen, which binds von Willebrand factor (vWF); vWF binds to glycoprotein (GP) Ib-IX-V on the platelet membrane that aids in initial platelet adhesion. Following injury, tissue factor is exposed, de-encrypted, and bound by factor VII, initiating the clotting cascade. With excessive activation of coagulation, injured patients can go on to develop disseminated intravascular coagulation (DIC), which is related to the exaggerated generation of thrombin and fibrin with consumption of platelets and coagulation factors. Brain injury has been associated with a high incidence of consumptive coagulopathy. Hulka *et al*. noted that after brain injury a DIC syndrome developed within 1–4 h; this condition can lead to consumptive coagulopathy that is associated with a higher frequency of death. In fact, in their series, 77% of brain-injured patients who died had a coagulopathy at the time of hospital admission.[8] Similarly, Faringer *et al*. found that $\geq$ 40% of exsanguinating patients with penetrating or blunt trauma and associated head injuries had abnormal coagulation parameters on admission while patients with blunt trauma and no brain injury did not have a coagulopathy.[9]

Certain risk factors have been correlated with the development of life-threatening coagulopathy. Cosgriff *et al*. showed that massively transfused trauma patients with the combination of an Injury Severity Score greater than 25, pH below 7.1, temperature less than 34°C, and systolic blood pressure $\leq$ 70 mmHg have a 98% likelihood of developing a life-threatening coagulopathy, defined as a prothrombin time (PT) or partial thromboplastin time (PTT) greater than or equal to 2 times normal. Patients with none of these risk factors had a 1% chance of developing a life-threatening coagulopathy.[10]

Severe injury is associated with the presence of coagulopathy at the time of hospital admission and with poor outcomes (Fig. 2).[5,11] In a retrospective review of 1,088 trauma patients over a 5-year period, 24.4 % of patients had a coagulopathy on admission defined as PT, activated partial thromboplastin time (APTT), or thrombin time (TT) greater than 1.5 times normal. Patients with a coagulopathy on admission had a significantly higher mortality rate than those with normal clotting on admission, (46% versus 10.9%).[11] In a similar review of trauma patients, MacLeod and colleagues showed that abnormal PT (> 14 s) and PTT (> 34 s) on admission were independent predictors of mortality. They concluded that an abnormal admission PT increases the adjusted odds of dying by 35% and that an abnormal admission PTT increases the adjusted odds of dying by 326%.[5] These numbers are consistent with the current military

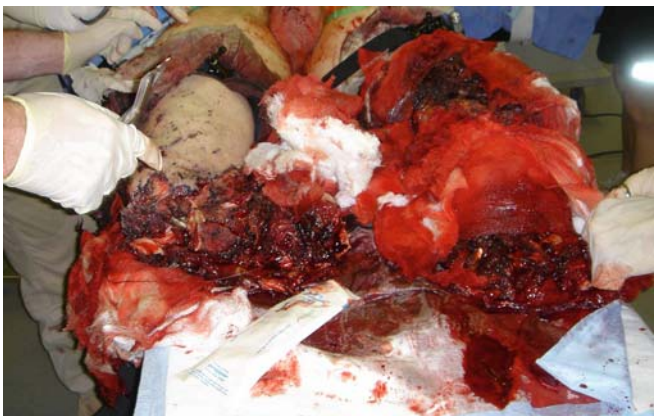

Figure 2. Severely injured patients can present with coagulopathy at the time of hospital admission. This soldier arrived in hemorrhagic shock and required massive transfusion with packed red blood cells (pRBC), coagulation products, and whole blood. Tourniquets were placed on the patient's thighs in the field to minimize blood loss.

experience in Operation Iraqi Freedom (OIF). In a review of 243 massively transfused (>10 U pRBC) casualties in Baghdad with an International normalized ratio (INR) >1.5 and decreased platelets on admission, the mortality rate was 30%. Those that were massively transfused with an admission INR < 1.5 had a mortality rate of 5%.

PATHOPHYSIOLOGY OF COAGULOPATHY AFTER TRAUMA

Hypothermia

Hypothermia has been a well-described cause of trauma-related coagulopathy. Hypothermia, defined by a core body temperature < 35°C, can occur from numerous sources. The patient can lose heat by convection and radiation with exposure in the field or trauma bay or by evaporative losses when wearing wet clothing. Reduced heat production occurs from decreased oxygen consumption during hemorrhagic shock. Operative intervention results in further heat loss from peritoneal and pleural surfaces. Fluid resuscitation results in a large potential for heat loss.[13] This can be quantified by the equation

$$\text{Heat} = \text{mass} \times \text{specific heat} \times (T_{body} - T_{fluid}) \quad .$$

Given a specific heat of water of 4.19 kJ/kg per degree, 1 liter of 25°C crystalloid infused in a normothermic patient would result in a heat loss of 50.3 kJ. This heat loss exceeds the heat that can be returned to the patient by conventional methods in 1 h.[13] This demonstrates the potential for tremendous heat loss with large scale resuscitation.

Hypothermia acts primarily on platelet activation and adhesion by inhibiting the interaction between von Willebrand factor with platelet glycoprotein Ib-IX-V complex,[14] but it also slows the metabolic rate of coagulation factor enzymes.[15] Ferrara *et al.* studied 45 trauma patients and found that hypothermia ($T \leq 34°C$) occurred in 80% of non-survivors and 36% of survivors. Clinically significant bleeding occurred in hypothermic and acidotic patients despite adequate blood, platelet, and plasma replacement.[16] Johnston *et al.* found that at 35°C, without dilution, there was a decrease in all coagulation factors. Factors XI and XII were only functioning at 65% of normal at this temperature, and at 32°C their activity was reduced to 17% and 32%, respectively.[17]

Acidosis

Metabolic acidosis is commonly seen in patients following trauma. The development of acidosis mainly affects coagulopathy by inhibiting the activities of the enzyme complexes on lipid surfaces. Meng *et al.* noted when the pH is reduced from 7.4 to 7.0, the activity level of FVIIa was reduced by 90%; FVIIa/TF complex, by 55%; and the rate of prothrombin activation by FXa/FVa complex, by 70%.[18] The activity of these coagulation factor complexes depends on their interaction with the negatively charged exposed phospholipids on the surface of activated platelets that are affected by increasing concentrations of hydrogen ions.[19] Temperature had a lesser effect on the enzymes, only reducing their activity by 10% for each 1°C decrease in temperature.[18] In a swine study, Martini *et al.* showed that acidosis alone (pH 7.1) and when combined with hypothermia (T = 32°C) increased splenic bleeding time by 41% and 72%, respectively. Similar findings were noted when they examined the affects of acidosis and hypothermia on thrombin generation. Thrombin plays a central role in activating cofactors, platelets, and enzymes, and in cleaving fibrinogen to fibrin. Acidosis was found to have a profound inhibitory affect on the thrombin generation rate that was increased when combined with hypothermia (Fig. 3).[20]

Resuscitation with crystalloid fluid has also been associated with the development of worsening acidosis. Following the Stewart model of acid base equilibrium, the administration of solutions with supraphysiologic levels of chloride relative to sodium results in a decreased strong ion difference (SID) (Na + K + Ca + Mg − Cl − lactate). This decreased SID causes further dissociation of H^+ from H_2O to maintain charge neutrality and therefore a decreased pH. Because of its supraphysiologic levels of chloride (154 mEq/l), normal saline (NS) has been

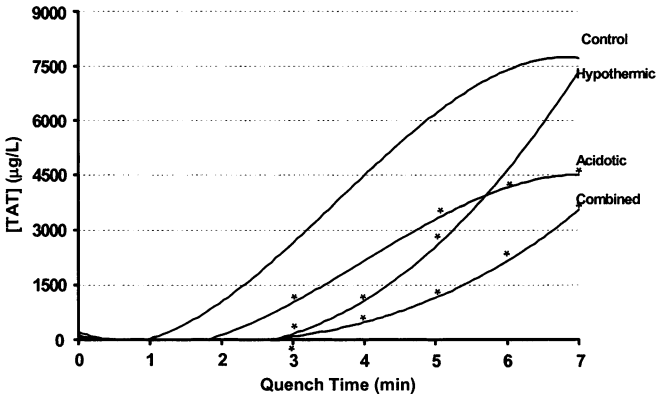

Figure 3. Thrombin generation rate in blood samples measured as thrombin-antithrombin III (TAT) complex concentration. The TAT concentration was measured in sample aliquots at time 0 (sample withdrawal) and at 1-min intervals thereafter to determine thrombin generation with time in each sample. $^*P < 0.05$, different from normal value at the same quench time point. Reprinted with permission from Martini WZ *et al.*, Independent contributions of hypothermia and acidosis to coagulopathy in swine. J Trauma 2005;58:1002–1010.

associated with hyperchloremic acidosis. Waters *et al.* found that the use of NS in patients undergoing abdominal aortic aneurysm repair resulted in the use of significantly more blood products, suggesting that it may have a harmful effect on the coagulation system.[21]

Hemodilution

Hemodilution of coagulation products can have a profound effect on the development of coagulopathy. Several factors can lead to the dilution of the body's coagulation factors. Direct loss of coagulation factors through hemorrhage can quickly reduce the body's small stores of fibrinogen (10 g) and platelets (15 ml).[20] Dilutional coagulopathy can then develop when these losses are replaced with fluids that do not contain clotting factors. Dilution often starts in the pre-hospital setting when crystalloids are given en route to the trauma center, followed by pRBCs in the trauma bay before laboratory test results become available. Abnormal results trigger the request for Fresh frozen plasma (FFP), which takes another 20–30 min to thaw resulting in a further delay to correct the ongoing coagulopathy. This cycle perpetuates itself with delays in diagnosis followed by treatments that only assist in further development of dysfunctional clotting capabilities.

Diagnosis of Coagulopathy

The clinical diagnosis of coagulopathic bleeding can be made based on generalized non-surgical bleeding from

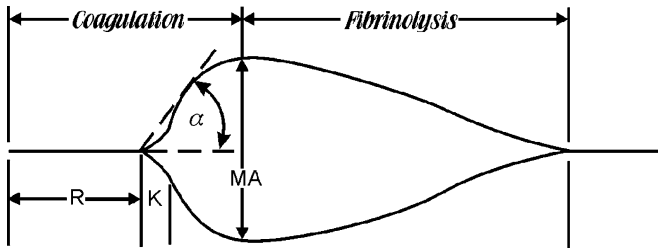

Figure 4. Thromboeslastograph (TEG) tracing. The reaction time (R) represents the time to onset of clot formation. K time is a measure of the speed to reach a certain level of clot strength. α angle represents the rate of clot formation. The maximum amplitude (MA) measures the clot strength. Reprinted with permission from Kiraly, J Trauma 2006;61:57–64.

wounds, serosal surfaces, skin edges, and vascular access sites. The ability to recognize this phenomenon is important since it indicates marked coagulopathy.

The laboratory diagnosis of coagulopathy optimally depends on simple, reliable, and rapid point of care tests that allow the physician to manage these severely injured patients. The current standard tests for coagulation parameters take time and may not truly reflect the patient's coagulation status. Patients who are actively bleeding and receiving blood products are in a constant state of flux with respect to coagulation parameters, and delays in obtaining results signify that the tests may not reflect the coagulation status of the patient.

In vivo coagulation depends on the interaction between platelets and coagulation factor enzymes. The PT and PTT are performed on platelet-poor plasma and do not evaluate the cellular interactions of clotting. In addition, PT and PTT values do not reflect hypothermia- induced coagulopathy because the samples are warmed to 37°C before measurement. Standard platelet and fibrinogen assays give numerical values but fail to provide information on function. The iSTAT hand held analyzer (Abbott Laboratories, Abbott Park, IL) is an alternative to standard laboratory measurement of PT that uses whole blood and can be done rapidly in the trauma bay. At present it is limited to testing activated clotting time (ACT) and PT/INR.

In contrast to the above-mentioned tests, the Thrombelastograph (TEG) analyzer® provides functional evaluation of overall coagulation on whole blood. This assay is performed at the bedside using 360 μl of whole blood at the same temperature as the patient. The TEG® measures the clotting time (R value), clot formation (α angle), clot strength (MA: maximum amplitude), and clot lysis (LY 30) (Fig. 4). The R value or reaction time represents the time to onset of clot formation. Elongation of the R represents a deficiency of coagulation factors. The α angle represents the rate of fibrin build-up

and crosslinking. This parameter is affected by fibrinogen function and, to a lesser degree, platelet function. The MA measures the clot strength and is affected primarily by platelets and, to a lesser degree, fibrinogen. The TEG® has been shown to be a more sensitive measure of coagulation disorders than standard coagulation measures.[22] A study investigating the use of TEG in the initial assessment of trauma patient coagulation looked at 69 adult blunt trauma patients. Forty-five patients (65%) were found to be hypercoagulable and 7 patients (10%) were hypocoagulable on TEG. All PT and PTT values were normal in the hypocoagulable group, except in one patient who had elevated PT and PTT levels. Six of the seven patients who were hypocoagulable by TEG® received blood transfusions. Only ISS and TEG® were predictive of early transfusion in these patients.[23]

A large volume of literature exists describing the use of TEG® in various settings to include trauma, transplant, cardiac surgery, routine assessment of coagulopathy, and hemophilia. Despite its obvious advantages, TEG has not become the standard of care for measurement of coagulopathy. As a point of care test, whole blood samples must be run within 3–4 min of collection, necessitating the presence of machines in multiple critical areas of the hospital as opposed to a central laboratory location. These machines are subject to the same quality-control regulations as other laboratory equipment. Centrally located TEG machines can be kept in the hospital laboratory but necessitates the test to be performed on citrated blood to prevent clotting during transport. Zambruni *et al.* compared native blood with citrated blood samples and noted the TEG parameters were affected by citrate storage.[24] Differences due to patient age and gender and recent reports concerning blood collection sites, sample stability, and repeat sampling have been raised.[24–30] In order to perform TEG testing, time must be invested in teaching hospital staff in the proper technique and use of the machine to assure valid and reproducible results.

Prevention and Early Treatment of Coagulopathy

In order to disrupt the bloody vicious cycle, restoring normal physiology involves aggressive re-warming, correction of acidosis, effective shock resuscitation, and reversal of coagulopathy. With the damaging effects of hypothermia established, surgical and critical care procedures to limit hypothermia have become routine. The trauma bay, operating room, or intensive care suite should be warmed. The patient should be kept dry with warmed blankets or thermal air convection blankets after completion of a secondary exam. Fluids and blood products should be given with a warming device. Continuous arteriovenous re-warming can be used for rapid warming (Fig. 5). This technique can re-warm a hypothermic patient (T < 35°C) in approximately 40 min.[31] It involves placement of introducer catheters in the femoral artery and vein forming a closed circuit powered by the patient's cardiac output. Blood is forced out of the femoral catheter trough the Level 1® warmer and back through the femoral vein catheter. This technique has been shown to reduce early mortality and resuscitation requirements in severely injured trauma patients.[32]

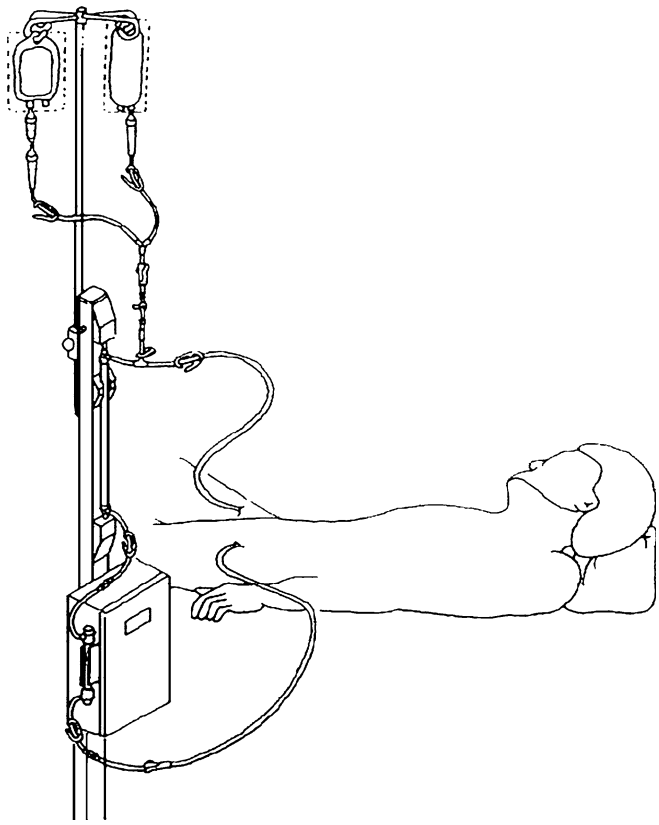

Figure 5. Set-up of continuous arteriovenous rewarming. This requires cannulation of the femoral artery and vein. Blood is circulated through the Level 1® warmer by the patient's blood pressure and returns through the femoral vein in a closed circuit system. Reprinted from Gentilello LM. Practical approaches to hypothermia. In Maull KI, Cleveland HC, Feliciano DV, *et al.*, editors, Advances in Trauma and Critical Care, vol. 9. St. Louis, Mosby, 1994:39–79, with permission from Elsevier.

Close attention to the choice of fluid used for resuscitation can help avoid coagulopathy. To avoid hyperchloremic acidosis, fluids with supraphysiologic concentrations of chloride should be avoided. Lactated Ringer's solution (LR) contains a more physiologic con-

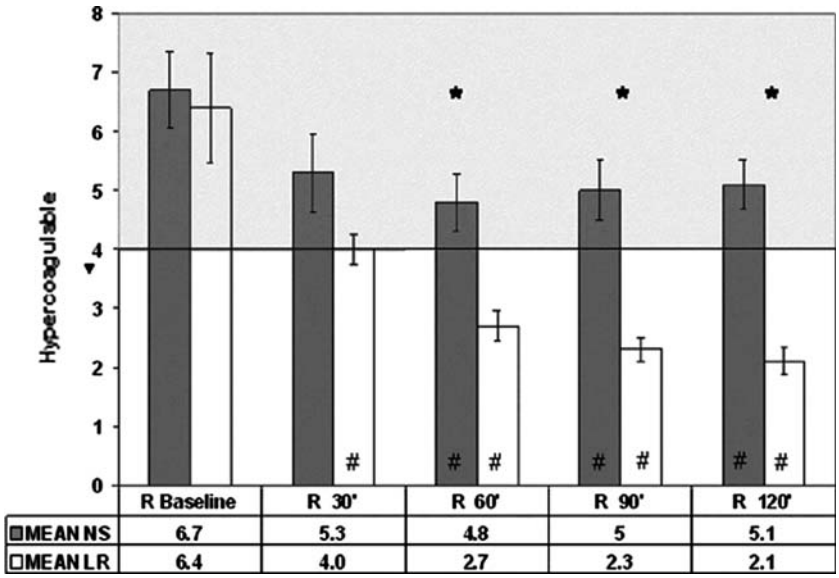

Figure 6. TEG R values at time intervals after injury in NS and LR groups. An asterisk indicates a significant difference ($P < 0.05$) between groups at that time interval. A pound sign indicates a significant difference from the baseline value ($P < 0.05$). The shaded area indicates normal ranges. Reprinted with permission from Kiraly: J Trauma 2006;61:57–65.

centration of chloride (109 mEq/l) than normal saline (NS; 154 mEq/l). Using an uncontrolled hemorrhagic shock model in swine, Kiraly *et al*. showed that resuscitation with NS compared with LR produces a relative hypocoagulable state following trauma and it resulted in increased blood loss (Fig. 6).[33]

The use of artificial colloids like hetastarch and dextran solutions has also been associated with the development of coagulopathy. Hetastarch solutions with high mean molecular weights, a large degree of substitution of hydroxyethyl groups per glucose unit, and a high C2/C6 ratio suppress coagulation more than solutions with more rapidly degradable low molecular weight colloids in vivo.[34–36] Various mechanisms including a reduction in von Willebrand factor, platelet dysfunction, reduced factor VIII levels, and interaction with fibrinogen have been hypothesized to produce this coagulopathy.[37]

Martin *et al*. compared the effects of Hextend® (BioTime, Inc., Berkeley, CA), a colloid containing 6% hetastarch in a balanced lactated buffered solution, LR and Hespan® (Bristol Myers Squibb, NY, NY), which is hetastarch in normal saline, in patients undergoing noncardiac surgery with an expected blood loss > 500 ml. They found that patients receiving Hespan developed coagulopathy during surgery while patients receiving Hextend or LR did not.[38] Using TEG, Gan *et al*. also demonstrated that Hextend had a more favorable coagulation profile compared to Hespan® in patients undergoing major surgery. Patients receiving Hespan had delayed onset of clotting as measured by the R time compared to patients receiving Hextend. The delay was more pronounced in patients receiving ≥ 20 ml/kg of fluids than those receiving ≤ 20 ml/kg. There are two possible explanations for this phenomenon. First, Hextend contains calcium levels similar to those found in blood (10 mg/dl), whereas Hespan contains none. Calcium is an essential cofactor in the coagulation cascade. In addition, the chloride content is lower in Hextend (124 mEq/l versus 154 mEq/l), and the presence of a buffered lactate results in less acidosis, further facilitating clotting.[39] The clinical impact of colloids on hemostasis remains unclear, and there are no formal guidelines for their use.

Small-volume resuscitation with hypertonic saline (HS) is attractive during hemorrhagic shock because it results in rapid expansion of intravascular volume. Concern over the use of HS developed after studies indicated that its use aggravated bleeding in uncontrolled hemorrhage.[40–42] In an in vitro study, Reed *et al*. showed anticoagulant effects of hypertonic saline on PT, PTT, and platelet aggregation when 10% or more of plasma volume was replaced by HS. They did not see these effects with the smaller volumes necessary to produce hemodynamic improvements.[43] Wilder *et al*. demonstrated prolonged PT and thrombin time when only 5% of plasma volume was replaced with hypertonic saline.[44] In contrast to these findings, Watters *et al*. showed in an uncontrolled hemorrhagic shock model in swine that, after delivery of a 250 ml bolus of different concentrations of HS and HS with 6% dextran, animals were hypercoagulable by TEG clotting time (R value) 90 min after receiving the bolus.[45] Further in vivo trials are needed to clinically correlate these findings, but with ongoing losses of coagulation factors it is important to be aware of these fluids' potential anticoagulation effects.

Damage-control Resuscitation

The principles of damage-control surgery include rapid control of hemorrhage and contamination, with early completion of the operation with a goal to restore normal physiology as opposed to normal anatomy. These principles have decreased mortality in the severely injured patient, and damage control has become standard surgical doctrine. These concepts can be extended to include the resuscitation phase of trauma care. Damage-control resuscitation (DCR) involves two components: hypotensive resuscitation and hemostatic resuscitation. Hypotensive resuscitation is a concept that dates back to World Wars I and II and was resurrected in the early 1990s. It involves fluid administration to a safe but lower than normal blood pressure until operative control of bleeding can be established. The goal is to minimize re-bleeding by dislodging the blood clot while maintaining perfusion to the tissues. It has been studied in animal and human trials, and shows promise as a potential alternative to traditional resuscitative strategies.[46–54] A definitive hypotensive resuscitation strategy has not been established. Hemostatic resuscitation employs blood components early in the resuscitation process to restore both perfusion and normal coagulation function, while minimizing crystalloid use. This prevents further dilution of already deficient coagulation factors.

Transfusion of blood products such as fresh frozen plasma, cryoprecipitate, and platelet concentrate can be used to treat coagulopathy. Unfortunately, stored platelets demonstrate decreased thrombotic function due to a decrease in expression of high-affinity thrombin receptors during platelet storage.[55] Using a three-compartment dynamic computer simulation, Hirshberg *et al*. showed that trauma patients with exsanguinating hemorrhage should receive fresh frozen plasma with the first units of pRBC to avoid dilutional coagulopathy.[56] They recommended using a FFP:pRBC ratio of 2:3. Even more aggressive FFP transfusion was suggested by Hewson *et al*. after they performed a retrospective review of 68 massively transfused patients. In patients with major bleeding, they recommended giving FFP and pRBC at a ratio of 1:1 to avoid dilutional coagulopathy.[57] The process of DCR in the military setting involves rapid diagnosis and control of surgical bleeding, avoiding re-bleeding, early use of rFVIIa, use of thawed plasma available at the time of patient arrival, transfusion of pRBC:FFP ratio of 1:1, frequent cryoprecipitate and platelet transfusion, as well as early consideration of FWB transfusion.

A retrospective review of DCR in a small number of patients compared to a group using standard resuscitation measures showed normalization of INR, decreased use of crystalloid fluid, and a significant reduction in the ratio of crystalloid to pRBC (0.4 ± 1.1 versus 1.3 ± 0.9) and pRBC to FFP (1.3 ± 2.3 versus 2.3 ± 1.8) (unpublished data). These measures are actively being implemented in the combat setting and they are likely to affect civilian management in the near future.

Fresh Whole Blood Transfusion

Because of the complexity of blood banking in the civilian setting, the use of FWB is rare. However, its use in the combat scenario has been well-described since World War I. Forward military surgical teams rely on soldier donors, or a walking blood bank, when their supplies are depleted or when a coagulopathic patient requires blood products that are unavailable. In OIF, 13% of all transfused patients have received FWB.[58] Fresh whole blood has been shown to correct dilutional coagulopathy, with evidence that a single unit of FWB has the hemostatic effect of 10 units of platelets.[55,59] In a retrospective review of FWB use in patients requiring massive transfusion at a U.S. forward deployed hospital, transfusion of a single unit of FWB resulted in significant improvements in hemoglobin concentration (9.0 ± 2.6 to 10.7 ± 1.9 g) and INR (2.0 ± 1.1 to 1.6 ± 0.9).[58] In another retrospective review, FWB use in addition to stored blood products resulted in a 15% absolute reduction and a 39% relative risk reduction in mortality compared to a similar group of combat casualties who received stored blood products alone.

A 500-ml unit of FWB has a hematocrit of 38%–50%, 150,000–400,000 platelets per microliter, and 100% activity of clotting factors diluted only by a small amount of anticoagulant. Current blood products consist of pRBC (335 ml, HCT 55%), platelets (50 ml, 5.5×10^{10} platelets) and FFP (275 ml, 80% coagulation factor activity). Combining these products results in 660 ml of fluid with a hematocrit of 29%, 88,000 platelets per microliter, and 65% coagulation factor activity.[58] Although no defined protocol has been established, FWB has been proven to be safe and beneficial in the military setting, and consideration should be given to reintroducing its use in civilian trauma centers.

Recombinant Activated Factor VII for Coagulopathic Bleeding

Recombinant activated factor VII (rFVIIa; Novoseven®, Novo Nordisk A/S, Bagsvaerd, Denmark) has been used

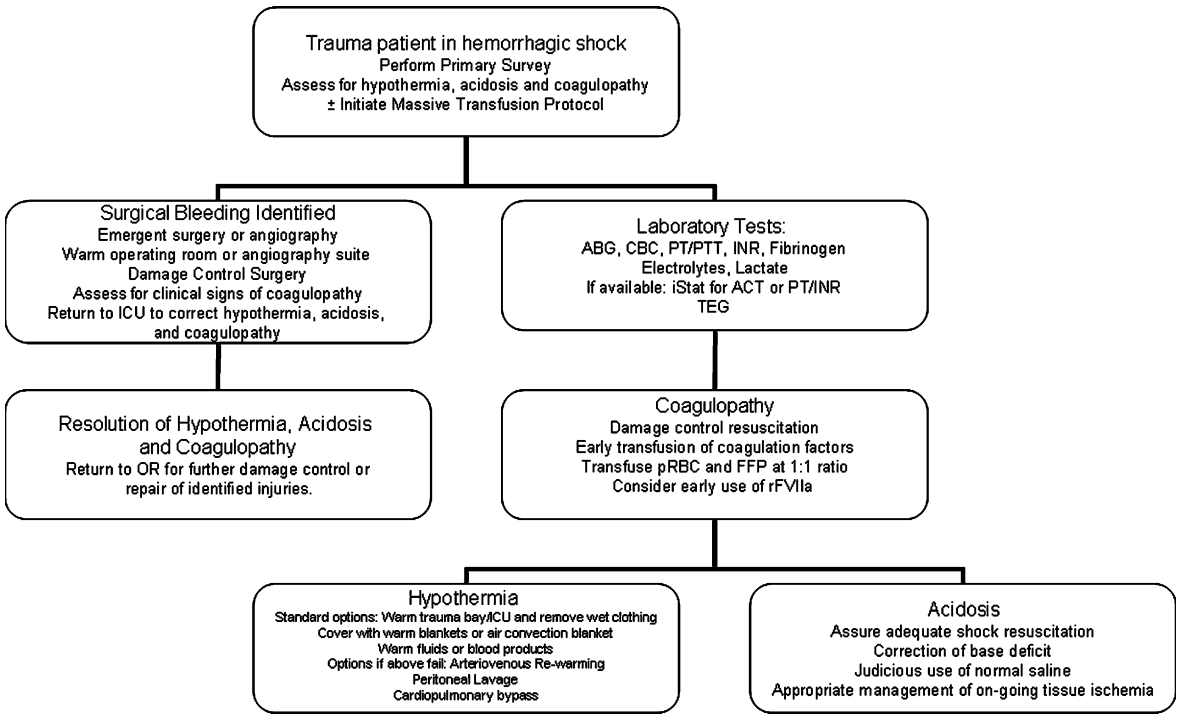

Figure 7. Diagnosis and treatment strategies of coagulopathy in trauma patients with hemorrhagic shock. It is imperative to continually assess the patient for the resolution of coagulopathy, acidosis, and hypothermia after the initiation of treatment. Implementation of more invasive maneuvers may be required if standard procedures fail.

to treat coagulopathic bleeding in severely injured trauma patients. It is currently approved by the U.S. Food and Drug Administration for (1) treatment of bleeding episodes in patients with hemophilia A or B and inhibitors to Factor VIII or IX, and in patients with congenital Factor VII deficiency; (2) prevention of bleeding in surgical interventions or invasive procedures in hemophilia A or B patients with inhibitors and in patients with congenital Factor VII deficiency; and (3) acquired hemophilia. rFVIIa affects coagulation at the local site of injury where tissue factor and phospholipids are exposed. It functions by accelerating the tissue factor dependent or independent pathways and, in association with platelet surface interactions, results in increased thrombin production.[60,61] Considering its association with platelets, rFVIIa-induced coagulation appears to need the presence of functional platelets to form a stable clot.[62] Acidosis (pH < 7.1) but not hypothermia reduces its activity. Most published reports of its use in trauma have been anecdotal and retrospective case reports. Boffard *et al.* published the results of a double-blinded, phase II, multicenter, multinational, randomized controlled trial of its use in trauma patients. Factor rFVIIa was given to severely bleeding blunt and penetrating trauma patients. The need for pRBC transfusion and massive transfusion was significantly reduced in the blunt trauma group but not in the penetrating trauma group. There was no difference in mortality noted between the study group and the controls.[63] Exact dosing and repeat dosing of rFVIIa has not been established. A double blinded, multicenter, multinational phase III trial to study its efficacy in trauma patients is now enrolling patients.

CONCLUSIONS

In conclusion, hemorrhage continues to be a major cause of death following trauma. The most severely injured patients are coagulopathic on admission, and current resuscitation practices can exacerbate bleeding. Prevention or correction of hypothermia and acidosis should remain a priority during the initial evaluation and resuscitation. Judicious use of fluids and early replacement of coagulation factors during massive transfusion will help prevent hemodilution. Hypotensive resuscitation allows for adequate tissue perfusion while preventing further blood loss by dislodging established clots until operative control of bleeding is established. Early use of rFVIIa for ongoing bleeding from coagulopathy should also be considered (Fig. 7). Use of fresh whole blood transfusion has proven to be safe and beneficial in the military setting and further studies to evaluate its efficacy are ongoing.

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