REVIEW Scandinavian Journal of Surgery 103: 81–88, 2014

DAMAGE CONTROL RESUSCITATION IN TRAUMA

H. M. A. Kaafarani, G. C. Velmahos

Division of Trauma, Emergency Surgery and Surgical Critical Care, Massachusetts General Hospital & Harvard Medical School, Boston, MA, USA

ABSTRACT

Introduction: **Most preventable trauma deaths are due to uncontrolled hemorrhage.**

Methods: **In this article, we briefly describe the pathophysiology of the classical triad of death in trauma, namely, acidosis, hypothermia, and coagulopathy, and then suggest damage control resuscitation strategies to prevent and/or mitigate the effects of each in the bleeding patient.**

Results: **Damage control resuscitation strategies include body rewarming, restrictive fluid administration, permissive hypotension, balanced blood product administration, and the implementation of massive transfusion protocols.**

Conclusion: **Resuscitating and correcting the coagulopathy of the exsanguinating trauma patient is essential to improve chances of survival.**

Key words: Resuscitation; hemorrhage; consumption coagulopathy; blood component transfusion; wounds and injury; acidosis

INTRODUCTION

Trauma and injuries account for 38% of the surgical burden of disease, disproportionately affecting younger patients (1). In the United States, trauma ranks fifth as a cause of death in all patients but is the leading cause of death in patients 44 years or younger. Most preventable in-hospital deaths from trauma are due to uncontrolled hemorrhage and resultant coagulopathy (2). Therefore, developing effective strategies to surgically control hemorrhage, successfully resuscitate the bleeding patient, and adequately correct traumatic coagulopathy is essential to increase the chances of survival of trauma patients. In this article, we describe damage control resuscitation (DCR) as a strategic approach to the trauma patient who presents in extremis.

Correspondence:
Haytham M. A. Kaafarani, M.D., M.P.H.
Division of Trauma, Emergency Surgery and Surgical Critical Care
Massachusetts General Hospital & Harvard Medical School
165 Cambridge St
Suite 810
Boston, MA 02114
USA
Email: hkaafarani@partners.org

PATHOPHYSIOLOGY

The classically described lethal triad of trauma consists of hypothermia, acidosis, and coagulopathy. The close interplay of these physiological derangements in the bleeding trauma patient leads to exsanguination and death, if not immediately recognized and aggressively reversed.

HYPOTHERMIA

Hypothermia in the trauma patient is multifactorial. Postulated etiologies include (1) cold exposure and body heat loss at the scene of injury, during transport, and in the emergency room; (2) the rapid administration of cold treatment fluids; and (3) the anesthesia/sedation effect on those patients requiring endotracheal intubation. In addition, the anaerobic metabolism that often accompanies hemorrhage (and leads to lactic acidosis) is less exothermic than aerobic

metabolism, leading to less endogenous body heat production, thus exacerbating the patient's hypothermia. Hypothermia is classified as mild when the core body temperature is between 34°C and 36°C, moderate with a temperature between 32°C and 34°C, and severe when it decreases below 32°C.

Hypothermia increases bleeding by impeding platelet adhesion (due to decreased thromboxane production), dysregulating the coagulation factors and enzymes, and interfering with fibrinolysis (3). Such an in vivo effect of hypothermia on coagulopathy is often missed upon coagulation parameters testing (e.g. prothrombin, partial thromboplastin, and bleeding times), due to routine in vitro warming of the blood sample to a temperature of 37°C prior to running the tests. Clinically, hypothermia in the trauma patient contributes to worse coagulopathy, worse metabolic acidosis, and cardiac dysrhythmias and serious electrolyte disorders.

ACIDOSIS

For the patient in shock, metabolic acidosis results from inadequate tissue perfusion, and subsequent production of lactic acidosis through anaerobic metabolism. The acidosis is often exacerbated by the overuse of normal saline for resuscitation. Normal saline has supraphysiologic concentrations of chloride (154 mEq/L), leading to hyperchloremic metabolic acidosis. The activity of many coagulation factors, like most protein-based enzymes, is dependent on the pH of their milieu. Several studies reliably confirm decreased coagulation factors' activity with decreasing pH; for example, a pH decrease from 7.4 to 7.0 reduces the activity of factor VIIa by over 90% (4) and the activity of the factor Xa/Va complex by more than 70% (5). Clinically, the degree of base deficit (i.e. acidosis) and the lactate levels on admission to the trauma may strongly correlate with worse patient mortality (6, 7).

COAGULOPATHY

Coagulopathy in the trauma patient is complex and is usually a combination of (1) dilutional resuscitation-related coagulopathy (DC) (8) and (2) non-dilutional acute traumatic coagulopathy (ATC) (9–11). DC occurs because of hemodilution during the administration of intravenous crystalloid or colloid fluids. In an analysis of the German trauma registry database, the volume of fluid resuscitation administered was proportional to the incidence of coagulopathy: coagulopathy developed in 40% of patients who received more than 2 L of intravenous fluids, in 50% of those who received more than 3 L of fluids, and in 70% of patients who received more than 4 L of fluids (12). DC may also occur if inadequate volumes of fresh frozen plasma (FFP) are given during massive blood transfusion. ATC is early trauma-related coagulopathy that occurs before hemodilution of coagulation factors, and affects about one-third of major trauma patients. It is believed that ATC results mainly from direct activation of the protein C pathway by tissue injury and hypoperfusion (10, 11, 13, 14). Activated protein C is a serine protease that depletes plasminogen activators, inhibits the coagulation factors V and VIII, and thus prevents coagulation and enhances fibrinolysis.

DCR

HISTORY

In the last few years, there has been a paradigm shift in the management of the severely injured trauma patient. As our understanding of the nature of trauma-related coagulopathy evolved, and with the recent combat trauma experiences in Iraq and Afghanistan, the concept of DCR in trauma was born. The term "damage control" itself originated from World War II description of the US Navy's strategy to salvage sinking ships (15, 16). The—then—new strategy avoided immediate definitive repair of the damaged vessel, and focused instead on preserving only what was needed to return the ship safely back into the port (e.g. watertight integrity, propelling power) for eventual definitive repair.

DEFINITION

DCR is a systematic approach to the management of the trauma patient with severe injuries that starts in the emergency room and continues through the operating room and the intensive care unit (ICU). It is designed, along with damage control surgery, to promptly and aggressively reverse the lethal trauma triad of coagulopathy, acidosis, and hypothermia.

ALGORITHM

When combined with damage control surgery, DCR has been shown to improve 30-day patient survival (17). An algorithm that incorporates damage control surgery and DCR is suggested in Fig. 1 and emphasizes the five pillars of DCR: (1) body rewarming, (2) correction of acidosis, (3) permissive hypotension, (4) restrictive fluid administration, and (5) hemostatic resuscitation.

BODY REWARMING

Granted that hypothermia is better prevented than reversed, the patient's hypothermia should be addressed in conjunction with the efforts to correct the trauma-related coagulopathy. Rewarming the torso before the extremities is essential to prevent worsening hypotension and acidosis due to peripheral vasodilation. Depending on the rate of rewarming needed, and the severity of the patient's hypothermia, three strategies of rewarming can be adopted: (1) passive external rewarming (e.g. removal of wet clothing, warm blankets, raising the ambient temperature of room), (2) active external rewarming (e.g. forced air-warming devices), and (3) active internal core rewarming (e.g. heated intravenous fluids, blood and blood products, humidified and heated oxygen administration). More invasive interventions such as body immersion in warm water, body cavity (gastric, esophageal, pleural, peritoneal) lavage, endovascular warming, or placing the patient on cardiovascular bypass

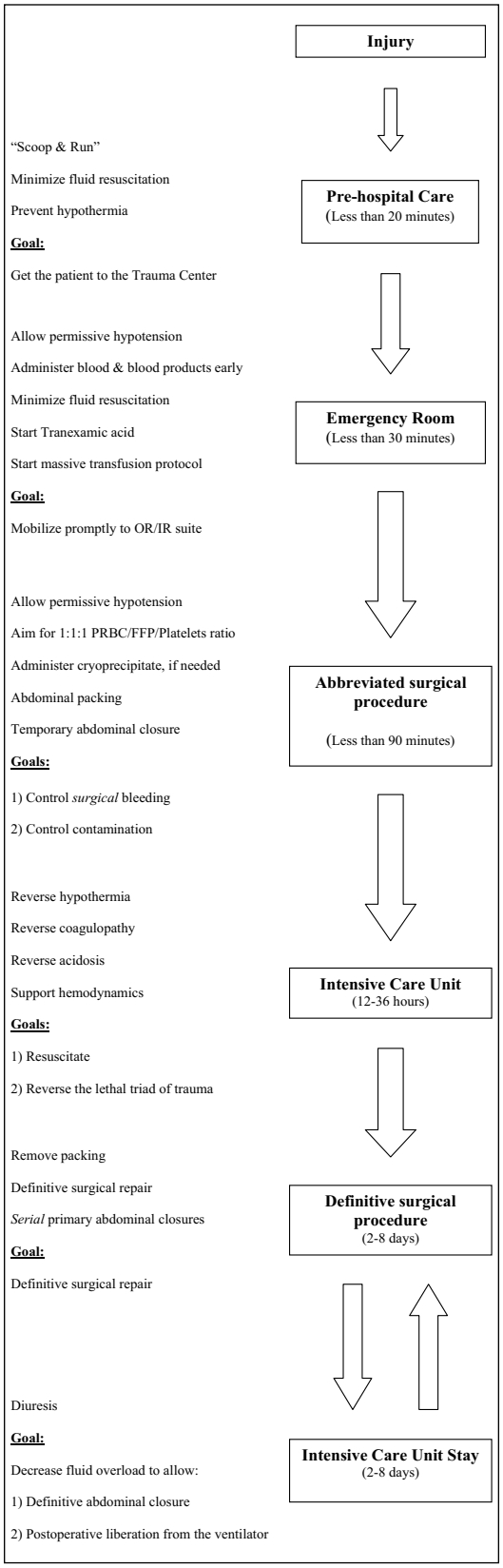

Fig. 1. Suggested damage control resuscitation and surgery algorithm. Times are estimates and should be tailored to the specific patient's needs and clinical situation.
OR: operating room; IR: interventional radiology; PRBC: packed red blood cell; FFP: fresh frozen plasma.

are rarely needed in the trauma patient, and their use is almost always prohibited by the unstable clinical status and ongoing bleeding. Persistence or quick relapse of the hypothermia despite best efforts should raise the suspicion for ongoing hemorrhage.

REVERSING ACIDOSIS

There currently exist no convincing data supporting the administration of bicarbonate or tris-hydroxymethyl aminomethane (THAM) to directly reverse metabolic acidosis in trauma patients, even when the pH is less than 7.2. Correction of the metabolic acidosis in the trauma patient is better achieved through aggressive blood and blood product resuscitation and vasopressor support until surgical control of hemorrhage is achieved, shock is reversed, and end-organ perfusion is restored. If direct reversal of severe acidosis is still sought, THAM has a slight advantage over bicarbonate in patients with hypernatremia or concomitant respiratory acidosis, as it does not involve excessive administration of sodium or the by-production of CO2 (18). Several endpoints of resuscitation need to be set a priori and followed diligently as vital signs alone are poor indicators of end-organ perfusion. Base deficit and lactate levels are reliable perfusion indices worth trending as markers of the adequacy of resuscitation; the initial levels at the time of presentation, as well as their clearance from plasma within the first few hours of resuscitation, correlate with mortality in trauma patients (19, 20).

PERMISSIVE HYPOTENSION

DEFINITION

Permissive hypotension is one of the central components of DCR. Permissive hypotension is the strategic decision to delay the initiation of fluid resuscitation and limit the volume of resuscitation fluids/blood products administered to the bleeding trauma patient by targeting a lower than normal blood pressure, usually a systolic blood pressure of 80–90 mmHg or a mean arterial pressure (MAP) of 50 mmHg.

RATIONALE

The theories behind permissive hypotension suggest that a lower target blood pressure (and thus a lower volume of resuscitation fluid) will improve patient outcomes by (1) decreasing the incidence and severity of dilutional coagulopathy and (2) avoiding the hypothetical "pop the clot" effect, which occurs when the fresh and unstable clot sealing a vascular laceration is dislodged when the intravascular pressure increases. A third potential advantage of restricting the volume of resuscitative fluids relates to the amelioration of the inflammatory cascade, which is exacerbated in response to exogenous fluids administration.

EVIDENCE

The earliest evidence for permissive hypotension in trauma patients came from a prospective trial

published in 1994 (21). In that pioneer but heavily critiqued study of penetrating torso trauma subjects, hypotensive patients who received no intravenous fluid administration prior to the operating room and were allowed a lower blood pressure in the pre-hospital and emergency room phases had a higher survival than those who were treated with more fluids targeting a "normal" systolic blood pressure (70% vs 62%, p = 0.04). The applicability of this strategy to all patients with hemorrhagic shock, including those who sustained blunt trauma, is controversial. Many subsequent randomized trials of hemorrhagic shock in humans or animals have not shown a clear mortality benefit (22–24) but had not identified any harm either. One study in rats suggested that transiently targeting a MAP of 50 mm Hg rather than 80 mm Hg results in less blood loss and improved animal survival (25). In that same study, permissive hypotension for longer than 90–120 min was associated with end-organ damage and worse animal outcomes. A randomized controlled trial is currently being conducted comparing the outcomes of targeting an intraoperative MAP of 50 versus 65 mmHg in patients with hemorrhagic shock undergoing surgery. The preliminary results of the first 90 patients were recently published, but the two arms of comparison are still not adequately matched in terms of injury severity; the preliminary data, however, suggest that permissive hypotension results in less blood product transfusion and intravenous fluids administration, an improved survival in the early postoperative phase, and a trend toward improved survival at 30 days (26). Permissive hypotension is better avoided in patients with evidence of major traumatic brain injury, as maintaining cerebral perfusion pressure is essential to limit secondary brain injury and further neuronal cells death in this patient population.

RESTRICTIVE FLUID ADMINISTRATION

In sharp contrast to the historic practice of "keeping the fluids running," the current evidence strongly suggests that the use of intravenous fluids in hemorrhagic shock patients should be minimized. Aggressive fluid resuscitation results in worse coagulopathy, an exaggerated trauma-related systemic inflammatory response syndrome (SIRS), an increased incidence of adult respiratory distress syndrome (ARDS), pulmonary edema, compartment syndrome, anemia, thrombocytopenia, pneumonia, electrolyte disturbances, and overall worse survival (27–32).

CRYSTALLOIDS VERSUS COLLOIDS

The type of fluid resuscitation used makes little difference. In a well-designed randomized controlled trial in all ICU patients, the overall 28-day mortality was similar between patients who were resuscitated with crystalloids versus those resuscitated with colloids (albumin) (33). The subset of trauma patients also had similar mortality rates, although a statistical trend for better survival with crystalloids versus albumin was observed. A subsequent ad hoc analysis of the same data found that albumin is associated with worse mortality in traumatic brain injury patients, compared with saline resuscitation (34). In the actively bleeding trauma patient, the resuscitation fluid of choice should be blood (and blood products), as we will delineate in the next section.

HYPERTONIC SALINE

Hypertonic saline (HTS) is commonly used in patients with traumatic brain injury in order to decrease intracranial cerebral pressure and to improve posttraumatic cerebral edema and oxygenation. Early small clinical studies suggested that HTS might be an ideal resuscitation fluid for all trauma patients: it works well as a volume expander (250 mL of 7.5% HTS is equivalent to 2–3 L of normal saline) and might have a favorable immune-modulating effect (35, 36). Two large randomized clinical trials that were recently designed and conducted by the Resuscitation Outcomes Consortium (ROC) attempted to study outcomes of resuscitation with HTS in traumatic brain injury patients and in patients with hypovolemic shock (37, 38). Both trials were stopped early after interim analysis for failure to show any favorable outcomes with HTS and for safety concerns. Therefore, we currently do not recommend HTS for resuscitation of trauma patients in shock.

HEMOSTATIC RESUSCITATION

BLOOD AND BLOOD COMPONENT TRANSFUSION

Unbalanced transfusion strategies in the exsanguinating trauma patient invariably lead to depletion of coagulation factors, exacerbation of dilutional coagulopathy, and more bleeding. Once the patient is recognized to have massive hemorrhage (fast rate of bleeding or requirement of more than 10 units of blood), early administration of blood products in addition to packed red blood cells (PRBCs) can help prevent trauma-related coagulopathy. Waiting for the classical coagulation parameters (prothrombin time (PT), partial thromboplastin time (PTT), platelets, and fibrinogen) to tailor transfusions may have deleterious effects, as the amount of blood transfusion needed in the trauma patient independently correlates with a higher incidence of ARDS, worse SIRS, poorer outcomes, and overall worse survival (39–41). One of the main pillars of DCR is early and aggressive transfusion of blood products aiming for a ratio of PRBCs, FFP, and platelets that approximates 1:1:1. The pioneering data for a balanced ratio of PRBCs and FFPs came from military experience, where the survival of combat hospital patients receiving variable ratios of FFP:PRBC was studied (42). In this retrospective study, the survival of patients receiving FFPs in a 1:8 ratio compared to PRBCs was dramatically higher than those receiving FFPs in a 1:1.4 ratio (92.5% vs 37%, $p < 0.001$). Most subsequent studies concurred that early FFP and blood products administration was beneficial in hemorrhaging patients, although controversy persists on the ideal transfusion ratio (43–53). One of the main criticisms of these retrospective studies lies

in the inherent selection (or survival) bias, where the patients received more FFPs because they had survivable injuries and thus lived longer with enough time to receive FFP (which typically requires about 40 min to thaw and prepare) and not *because* of the FFP (54–57). In an attempt to address this criticism of survival bias, a recent multicenter study found that high FFP/PRBC and platelet/PRBC ratios are associated with a survival benefit independent of the fluctuations of the time of administration of blood products, and concluded that the high component transfusion ratio survival benefit is not a mere selection bias (58). The data for early and aggressive platelet and cryoprecipitate (fibrinogen) transfusion in the massively hemorrhaging patient are similarly retrospective but suggest improved survival (59–62). The benefit of high component transfusion ratios is not clear in patients who require transfusion of less than 10 units of PRBCs. Of note, Level 1 evidence is lacking on this issue. The ROC, sponsored by the National Institutes of Health, is currently conducting a large-scale, multicenter, prospective randomized study, comparing patients who receive 1:1 FFP:PRBC with those who receive 1:2.

MASSIVE TRANSFUSION PROTOCOLS

Massive transfusion is typically defined as a transfusion of 10 or more units of PRBCs within the first 24 h of injury. In practice, the high rate of bleeding of the trauma patient should be recognized early by the trauma or emergency room physician, and massive transfusion should be planned as early as possible following injury. A multicenter study of major trauma centers found that only 1.7% of admitted trauma patients require massive transfusion (63). The logistic coordination to rapidly obtain and efficiently deliver a large number of PRBCs, FFPs, platelets, and cryoprecipitate to the bedside of the exsanguinating patient moving from the ambulance to the emergency room, operating room, interventional radiology suite, and ICU is a daunting task. In major trauma centers, the development and implementation of systematic approaches to transfusion practices through the creation of massive transfusion protocols (MTPs) is crucial. In patients known or predicted to require massive transfusion, the prompt activation of a MTP not only leads to a more systematic, efficient, timely, and balanced delivery of blood and blood products, but can also result in overall *less* use of blood and improved patient outcomes and survival (64–67). The ideal MTP is created by joined efforts of the trauma, emergency room, and blood bank teams, and should clearly address the following critical steps: (1) who should activate the MTP, (2) when should the protocol be activated, (3) who is the MTP patient candidate, (4) the detailed logistical steps of activation, (5) the number of uncrossed PRBC, FFP, and platelets units to be immediately released, (6) the blood component ratio goal, (7) the ABO matching process, (8) the detailed logistical steps of transferring the released units to the patient's bedside, and (9) the end goals of resuscitation (e.g. surgical control of bleeding, stopping resuscitation efforts for futility). Fig. 2 represents the MTP currently used at the Massachusetts General Hospital and delineates the level of details that should be sought when creating such a protocol.

GOALS AND MONITORING

Initial waiting for abnormal coagulation tests before administration of blood products in the massively hemorrhaging trauma patient is inappropriate. Subsequent serial examinations with complete blood count (CBC), PT, PTT, fibrinogen, and platelet count can be used to tailor component therapy in order to achieve hemostasis. PRBCs should be given to target a hemoglobin >7 g/dL, FFPs to target an international normalized ratio (INR) <2, platelets to target a count >50,000, and cryoprecipitate to target a fibrinogen level >100 mg/dL. The use of thromboelastography-based protocols that assess the different aspects of clot formation and stability in a real time point-of-care output graph has been incorporated into some MTPs or suggested as an alternative to MTPs. Although promising, this methodology is lacking the multi-institutional rigorous data supporting its use (68–71).

HEMOSTATIC ADJUNCTS

Anti-fibrinolytic agents

Early administration of tranexamic acid (TXA), an anti-fibrinolytic agent, was shown in a large international, multicenter, randomized, placebo-controlled trial to slightly decrease the risk of death from bleeding (n = 20,211; relative risk (RR) = 0.85; 95% confidence interval (CI) = 0.76–0.96; p = 0.0077) (72). We therefore recommend the use of TXA in massively bleeding trauma patients, and incorporating it in MTPs. Other similar anti-fibrinolytic agents include aprotinin and aminocaproic acid.

Factor-concentrates

Convincing data on the use of recombinant factor VIIa or prothrombin complex concentrates (PCCs)—both initially derived for hemophiliac patients—in the massively bleeding trauma patients are still lacking and there does not appear to be a clear benefit from their use (73).

CONCLUSION

The successful resuscitation of the massively bleeding and unstable trauma patient will depend on effective trauma team leadership, identification of early trauma-related coagulopathy, sound decision-making in the emergency and operating rooms (74), and prompt implementation of a DCR and a damage control operative approach. DCR includes permissive hypotension, body rewarming, minimization of fluid resuscitation, and early balanced administration of blood and blood products.

Policy: To provide a mechanism to facilitate replacement of massive blood loss with appropriate blood and blood products within a clinically significant timeframe.

Protocol: Application of the Massive Transfusion Protocol requires a multidiscipline/multiservice practice based on clinical judgment and decision-making, clear communication patterns and strong cooperative efforts.

1. The decision to utilize the Protocol will be determined by one of the following appropriate trauma team members:
   a. Trauma/CC anesthesiologist
   b. Trauma staff attending
   c. EM staff attending
   d. Senior Trauma Resident
   e. EM 4 resident
   f. PGY 3 ED surgical resident

   NOTE: The protocol can be initiated at any time during the trauma patient's hospitalization, including prior to arrival to the MGH ED.

2. Appropriate candidates for this Protocol include:
   a. any patient with an initial blood loss of at least 40% of blood volume (estimated at 30 ml/kg), or in whom it is judged that at least 10 units of blood replacement is immediately required;
   b. any patient with a continuing hemorrhage of at least 250cc/hour (or 20 ml/kg/hr);
   c. any patient, when clinical judgment is made such that blood loss as identified in "A" and "B" is imminent.

3. If the protocol is initiated prior to the patient's arrival at the MGH, an 'Trauma Pack' should be utilized.

4. Once the decision is made to initiate the Massive Transfusion Policy, the appropriate physician needs to:
   a. Call Blood Bank 6-3623 or use red phone in emergency department.
   b. Provide the following information:
      (1) Patient's name
      (2) Patient's MRN
      (3) Location of patient
      (4) Products anticipated
      (5) Status of blood sample for typing
      (6) Plan for blood delivery (runner to pickup, other)
   c. Request on the telephone release of "4 units of Emergency Uncrossmatched RBCs" and send:
      (1) a Request slip with the patient's full name, MRN, location, and products requested;
      (2) a Pickup slip with the patient's full name, MRN, location, and products requested.

5. Blood Type:
   a. If no in-date blood sample exists, send a properly labeled, signed, and dated blood bank sample to Blood Bank for ABO typing.
   b. Release of FFP, Platelets, and ABO matching RBCs require that blood typing sample be received by the Blood Bank.

6. Administer an anti-fibrinolytic
   Based on RCT evidence, trauma patients have improved chance of survival if treated with a bolus and infusion of an antifibrinolytic within the 3 hours of injury.

7. Request set-up of additional Blood Products
   Send a Request Slip with the patient's full name, MRN, location and products requested.

8. Request release of additional Blood Products
   All requests for Release Of Blood require a Pick Up Slip with the patient's full name, MRN, and product requested.

9. The Clinical Team and the Transfusion Medicine service maintain joint responsibility for the success of the Massive Transfusion Protocol. A Transfusion Medicine Physician is available at all times by pager.

10. RBC Selection:
    a. At least 4 units of Emergency –release, uncrossmatched Group O Rh-negative RBC's will be available for immediate release to any patient.
    b. All patients will receive Rh negative cells as long as inventory is adequate. An effort will be made to provide Rh negative cells to females under age 50 as long as inventory is adequate. The laboratory will decide to switch the patient to Rh-positive RBCs based on the available inventory and the anticipated RBC requirement.
    c. Group O RBCs will be used until the patient's blood group is known after which the patient will be switched to group-specific RBCs.

11. Blood Component Requests:
    After the initial assessment, the clinical team should request more blood as follows:
    a. If hemorrhage appears controllable and if < 10 TOTAL units (or 40 ml/kg) are anticipated, the clinical team should order RBCs (in addition to the emergency-release 4 units); and send a properly labeled "Pick-up slip" for these units.
    b. If > 10 TOTAL units (or 40 ml/kg) are expected to be needed, the clinical team should request (in addition to the initial 4 emergency RBCs):
       (1) 10 RBCs
       (2) 10 FFP
       (3) 1 dose of platelets
       (4) For children, make size appropriate adjustments to the above request.
    c. Upon receipt of a properly labeled "Pick Up Slip" indicating the location (ED, OR, ICU, etc) the request will be filled and units issued ASAP. The blood bank will fill partial orders so as not to delay the entire order. For example, 6 RBCs and 4 FFP and 1 dose of platelets may be issued immediately and then followed by 4 RBCs and 6 FFP.
    d. It is the responsibility of the clinical team to insure that issued blood components will be promptly delivered to the bedside.

12. Blood component ratio during resuscitation:
    a. Target a ratio of 2 RBCs to 1 FFP (include cell saver in count of RBCs).
    b. Give 1 dose of platelets (eg, 6 units for an adult) for each blood volume resuscitation
    c. Adjust the platelet dose for children based on estimated blood volume.

13. Transport of the patient from the ED to the OR or to Radiology:
    a. It is ESSENTIAL that the clinical team communicate to the blood bank when the patient is being moved from the ED to the OR or to Radiology so that additional blood units, as available, will be directed to the proper location.
    b. Failure to communicate the movement of the patient will lead to delays in administration of blood components.

Note: The blood bank staff is instructed **NOT** to issue blood to two locations for one patient simultaneously.

14. Laboratory monitoring for on-going blood support in cases requiring > 10 units of RBCs (40 ml/kg):
    a. Transfusion support should be individualized for each patient.
    b. The following "general guidelines" apply:
       (1) Check H/H, Platelet count, INR, and Fibrinogen after each blood volume lost/infused.(80 ml/kg)
       (2) Include the number of "cell saver" units in the tally of packed RBCs.
       (3) Target a ratio of 2 RBCs to 1 FFP during the course of acute bleeding.
       (4) Anticipate fibrinolysis and treat with additional boluses of anti-fibrinolytics if there is ongoing diffuse bleeding.
       (5) Verify that the INR is < 2.5 and fibrinogen >100. Values outside these ranges may indicate systemic fibrinogenolysis, DIC, or failure to avoid hemodilution.
       (6) In the absence of platelet infusion, anticipate a halving of the platelet count with each blood volume resuscitation (80 ml/kg). Transfuse platelets to maintain an anticipated platelet count >50,000/uL.
       (7) A stat AST or ALT can be used to document shock liver (values >800) which is a poor prognostic sign and an independent indication for anti-fibrinolytic therapy.
    c. Monitor and treat abnormalities of ionized Ca++, K+, pH and temperature.

15. At the end of surgery, notify the ICU and the Blood Bank when leaving the OR on route to the ICU.
    a. Take a sufficient number of units of blood, not in a cooler, with the patient to cover the next 30 minutes of blood transfusion support.
    b. Return the residual units in the cooler to the Blood Bank.
    b. The blood bank will issue a fresh cooler of blood to the ICU according to an established hospital policy for moving unstable patients from OR to ICU..

16. Not all massive injured patients can be saved. The decision to withdraw support for the massively injured patient should be made by consensus of the treating team and with approval of the trauma attending responsible for the case. Considerations include likelihood of survival, nature of injuries, and impact of blood requirements on other patients in the hospital in need of blood support. Consultation with the senior blood bank physician on duty is welcome.

Fig. 2. A real example of massive transfusion protocols.
CC: critical care; EM: emergency medicine; PGY: postgraduation year; ED: emergency department; MGH: Massachusetts General Hospital; MRN: medical record number; FFP: fresh frozen plasma; RCT: randomized controlled trial; RBC: red blood cell; OR: operating room; ICU: intensive care unit; DIC: disseminated intravascular coagulation; AST: aspartate transaminase; ALT: alanine transaminase.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Debas HT, Gosselin R, McCord C et al: Chapter 67: Surgery. In: Jamison DT, Breman JG, Measham AR et al (Eds) Disease Control Priorities in Developing Countries, 2nd ed. World Bank, Washington, DC, 2006, pp. 1245–1260.
2. Evans JA, van Wessem KJ, McDougall D et al: Epidemiology of traumatic deaths: Comprehensive population-based assessment. World J Surg 2010;34(1):158–163.
3. Wolberg AS, Meng ZH, Monroe DM 3rd et al: A systematic evaluation of the effect of temperature on coagulation enzyme activity and platelet function. J Trauma 2004;56(6):1221–1228.
4. Meng ZH, Wolberg AS, Monroe DM, 3rd et al: The effect of temperature and pH on the activity of factor VIIa: Implications for the efficacy of high-dose factor VIIa in hypothermic and acidotic patients. J Trauma 2003;55(5):886–891.
5. Martini WZ, Pusateri AE, Uscilowicz JM et al: Independent contributions of hypothermia and acidosis to coagulopathy in swine. J Trauma 2005;58(5):1002–1009.
6. Tremblay LN, Feliciano DV, Rozycki GS: Assessment of initial base deficit as a predictor of outcome: Mechanism of injury does make a difference. Am Surg 2002;68(8):689–693.
7. Abramson D, Scalea TM, Hitchcock R et al: Lactate clearance and survival following injury. J Trauma 1993;35(4):584–588.
8. Tieu BH, Holcomb JB, Schreiber MA: Coagulopathy: Its pathophysiology and treatment in the injured patient. World J Surg 2007;31(5):1055–1064.
9. Brohi K, Singh J, Heron M et al: Acute traumatic coagulopathy. J Trauma 2003;54(6):1127–1130.
10. Davenport R: Pathogenesis of acute traumatic coagulopathy. Transfusion 2013;53(Suppl. 1):23S–27S.
11. Cohen MJ, Kutcher M, Redick B et al: Clinical and mechanistic drivers of acute traumatic coagulopathy. J Trauma Acute Care Surg 2013;75(1 Suppl. 1):S40–S47.
12. Maegele M, Lefering R, Yucel N et al: Early coagulopathy in multiple injury: An analysis from the German Trauma Registry on 8724 patients. Injury 2007;38(3):298–304.
13. MacLeod JB, Lynn M, McKenney MG et al: Early coagulopathy predicts mortality in trauma. J Trauma 2003;55(1):39–44.
14. Brohi K, Cohen MJ, Ganter MT et al: Acute traumatic coagulopathy: Initiated by hypoperfusion: Modulated through the protein C pathway? Ann Surg 2007;245(5):812–818.
15. Griffin A: A Ship to Remember. Howell Soskin Publishers, New York, 1943.
16. Gaynor F: The New Military and Naval Dictionary. Philosophical Library Publishers, New York, 1951.
17. Cotton BA, Reddy N, Hatch QM et al: Damage control resuscitation is associated with a reduction in resuscitation volumes and improvement in survival in 390 damage control laparotomy patients. Ann Surg 2011;254(4):598–605.
18. Hoste EA, Colpaert K, Vanholder RC et al: Sodium bicarbonate versus THAM in ICU patients with mild metabolic acidosis. J Nephrol 2005;18(3):303–307.
19. Hodgman EI, Morse BC, Dente CJ et al: Base deficit as a marker of survival after traumatic injury: Consistent across changing patient populations and resuscitation paradigms. J Trauma Acute Care Surg 2012;72(4):844–851.
20. Odom SR, Howell MD, Silva GS et al: Lactate clearance as a predictor of mortality in trauma patients. J Trauma Acute Care Surg 2013;74(4):999–1004.
21. Bickell WH, Wall MJ Jr, Pepe PE et al: Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. N Engl J Med 1994;331(17):1105–1109.
22. Dutton RP, Mackenzie CF, Scalea TM: Hypotensive resuscitation during active hemorrhage: Impact on in-hospital mortality. J Trauma 2002;52(6):1141–1146.
23. Skarda DE, Mulier KE, George ME et al: Eight hours of hypotensive versus normotensive resuscitation in a porcine model of controlled hemorrhagic shock. Acad Emerg Med 2008;15(9):845–852.
24. Turner J, Nicholl J, Webber L et al: A randomised controlled trial of prehospital intravenous fluid replacement therapy in serious trauma. Health Technol Assess 2000;4(31):1–57.
25. Li T, Zhu Y, Hu Y et al: Ideal permissive hypotension to resuscitate uncontrolled hemorrhagic shock and the tolerance time in rats. Anesthesiology 2011;114(1):111–119.
26. Morrison CA, Carrick MM, Norman MA et al: Hypotensive resuscitation strategy reduces transfusion requirements and severe postoperative coagulopathy in trauma patients with hemorrhagic shock: Preliminary results of a randomized controlled trial. J Trauma 2011;70(3):652–663.
27. Cotton BA, Guy JS, Morris JA Jr et al: The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies. Shock 2006;26(2):115–121.
28. Daugherty EL, Liang H, Taichman D et al: Abdominal compartment syndrome is common in medical intensive care unit patients receiving large-volume resuscitation. J Intensive Care Med 2007;22(5):294–299.
29. O'Mara MS, Slater H, Goldfarb IW et al: A prospective, randomized evaluation of intra-abdominal pressures with crystalloid and colloid resuscitation in burn patients. J Trauma 2005;58(5):1011–1018.
30. Giannoudis PV, Fogerty S: Initial care of the severely injured patient: Predicting morbidity from sub-clinical findings and clinical proteomics. Injury 2007;38(3):261–262.
31. Klein MB, Hayden D, Elson C et al: The association between fluid administration and outcome following major burn: A multicenter study. Ann Surg 2007;245(4):622–628.
32. Kasotakis G, Sideris A, Yang Y et al: Aggressive early crystalloid resuscitation adversely affects outcomes in adult blunt trauma patients: An analysis of the Glue Grant database. J Trauma Acute Care Surg 2013;74(5):1215–1221;discussion 1221–1222.
33. Finfer S, Bellomo R, Boyce N et al: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004;350(22):2247–2256.
34. SAFE Study Investigators: Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med 2007;357(9):874–884.
35. Junger WG, Coimbra R, Liu FC et al: Hypertonic saline resuscitation: A tool to modulate immune function in trauma patients? Shock 1997;8(4):235–241.
36. Deitch EA, Shi HP, Feketeova E et al: Hypertonic saline resuscitation limits neutrophil activation after trauma-hemorrhagic shock. Shock 2003;19(4):328–333.
37. Bulger EM, May S, Brasel KJ et al: Out-of-hospital hypertonic resuscitation following severe traumatic brain injury: A randomized controlled trial. JAMA 2010;304(13):1455–1464.
38. Bulger EM, May S, Kerby JD et al: Out-of-hospital hypertonic resuscitation after traumatic hypovolemic shock: A randomized, placebo controlled trial. Ann Surg 2011;253(3):431–441.
39. Charles A, Shaikh AA, Walters M et al: Blood transfusion is an independent predictor of mortality after blunt trauma. Am Surg 2007;73(1):1–5.
40. Dunne JR, Malone DL, Tracy JK et al: Allogenic blood transfusion in the first 24 hours after trauma is associated with increased systemic inflammatory response syndrome (SIRS) and death. Surg Infect (Larchmt) 2004;5(4):395–404.
41. Silverboard H, Aisiku I, Martin GS et al: The role of acute blood transfusion in the development of acute respiratory distress syndrome in patients with severe trauma. J Trauma 2005;59(3):717–723.
42. Borgman MA, Spinella PC, Perkins JG et al: The ratio of blood products transfused affects mortality in patients receiving

massive transfusions at a combat support hospital. J Trauma 2007;63(4):805–813.
43. Holcomb JB, Wade CE, Michalek JE et al: Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Ann Surg 2008;248(3):447–458.
44. Gunter OL Jr, Au BK, Isbell JM et al: Optimizing outcomes in damage control resuscitation: Identifying blood product ratios associated with improved survival. J Trauma 2008;65(3):527–534.
45. Cotton BA, Gunter OL, Isbell J et al: Damage control hematology: The impact of a trauma exsanguination protocol on survival and blood product utilization. J Trauma 2008;64(5):1177–1182;discussion 1182–1183.
46. Alam HB, Rhee P. New developments in fluid resuscitation. Surg Clin North Am 2007;87(1):55–72.
47. Kashuk JL, Moore EE, Johnson JL et al: Postinjury life threatening coagulopathy: Is 1:1 fresh frozen plasma: packed red blood cells the answer? J Trauma 2008;65(2):261–270;discussion 270–271.
48. Gonzalez EA, Moore FA, Holcomb JB et al: Fresh frozen plasma should be given earlier to patients requiring massive transfusion. J Trauma 2007;62(1):112–119.
49. De Biasi AR, Stansbury LG, Dutton RP et al: Blood product use in trauma resuscitation: Plasma deficit versus plasma ratio as predictors of mortality in trauma (CME). Transfusion 2011;51(9):1925–1932.
50. Brown LM, Aro SO, Cohen MJ et al: A high fresh frozen plasma: Packed red blood cell transfusion ratio decreases mortality in all massively transfused trauma patients regardless of admission international normalized ratio. J Trauma 2011;71(2 Suppl. 3):S358–S363.
51. Sperry JL, Ochoa JB, Gunn SR et al: An FFP:PRBC transfusion ratio >/=1:1.5 is associated with a lower risk of mortality after massive transfusion. J Trauma 2008;65(5):986–993.
52. Maegele M, Lefering R, Paffrath T et al: Red-blood-cell to plasma ratios transfused during massive transfusion are associated with mortality in severe multiple injury: A retrospective analysis from the Trauma Registry of the Deutsche Gesellschaft für Unfallchirurgie. Vox Sang 2008;95(2):112–119.
53. Shaz BH, Dente CJ, Nicholas J et al: Increased number of coagulation products in relationship to red blood cell products transfused improves mortality in trauma patients. Transfusion 2010;50(2):493–500.
54. Rajasekhar A, Gowing R, Zarychanski R et al: Survival of trauma patients after massive red blood cell transfusion using a high or low red blood cell to plasma transfusion ratio. Crit Care Med 2011;39(6):1507–1513.
55. McGwin G Jr, Melton S, Kerby J et al: Survival bias revisited. J Trauma Acute Care Surg 2013;74(1):345–346.
56. Nascimento B, Callum J, Rubenfeld G et al: Clinical review: Fresh frozen plasma in massive bleedings—More questions than answers. Crit Care 2010;14(1):202.
57. Scalea TM, Bochicchio KM, Lumpkins K et al: Early aggressive use of fresh frozen plasma does not improve outcome in critically injured trauma patients. Ann Surg 2008;248(4):578–584.
58. Brown JB, Cohen MJ, Minei JP et al: Debunking the survival bias myth: Characterization of mortality during the initial 24 hours for patients requiring massive transfusion. J Trauma Acute Care Surg 2012;73(2):358–364;discussion 364.
59. Phan HH, Wisner DH. Should we increase the ratio of plasma/platelets to red blood cells in massive transfusion: What is the evidence? Vox Sang 2010;98(3 Pt 2):395–402.
60. Brown LM, Call MS, Margaret Knudson M et al: A normal platelet count may not be enough: the impact of admission platelet count on mortality and transfusion in severely injured trauma patients. J Trauma 2011;71(2 Suppl. 3):S337–S342.
61. Inaba K, Lustenberger T, Rhee P et al: The impact of platelet transfusion in massively transfused trauma patients. J Am Coll Surg 2010;211(5):573–579.
62. Stinger HK, Spinella PC, Perkins JG et al: The ratio of fibrinogen to red cells transfused affects survival in casualties receiving massive transfusions at an army combat support hospital. J Trauma 2008;64(2 Suppl.):S79–S85;discussion S85.
63. Como JJ, Dutton RP, Scalea TM et al: Blood transfusion rates in the care of acute trauma. Transfusion 2004;44(6):809–813.
64. Tan JN, Burke PA, Agarwal SK et al: A massive transfusion protocol incorporating a higher FFP/RBC ratio is associated with decreased use of recombinant activated factor VII in trauma patients. Am J Clin Pathol 2012;137(4):566–571.
65. Dente CJ, Shaz BH, Nicholas JM et al: Improvements in early mortality and coagulopathy are sustained better in patients with blunt trauma after institution of a massive transfusion protocol in a civilian level I trauma center. J Trauma 2009;66(6):1616–1624.
66. Ball CG, Dente CJ, Shaz B et al: The impact of a massive transfusion protocol (1:1:1) on major hepatic injuries: Does it increase abdominal wall closure rates? Can J Surg 2013;56(5):E128–E134.
67. Khan S, Allard S, Weaver A et al: A major haemorrhage protocol improves the delivery of blood component therapy and reduces waste in trauma massive transfusion. Injury 2013;44(5):587–592.
68. Kashuk JL, Moore EE, Wohlauer M et al: Initial experiences with point-of-care rapid thrombelastography for management of life-threatening postinjury coagulopathy. Transfusion 2012;52(1):23–33.
69. Plotkin AJ, Wade CE, Jenkins DH et al: A reduction in clot formation rate and strength assessed by thrombelastography is indicative of transfusion requirements in patients with penetrating injuries. J Trauma 2008;64(2 Suppl.):S64–S68.
70. Cotton BA, Faz G, Hatch QM et al: Rapid thrombelastography delivers real-time results that predict transfusion within 1 hour of admission. J Trauma 2011;71(2):407–414;discussion 414–417.
71. Johansson PI, Sørensen AM, Larsen CF et al: Low hemorrhage-related mortality in trauma patients in a Level I trauma center employing transfusion packages and early thromboelastography-directed hemostatic resuscitation with plasma and platelets. Transfusion 2013;53:3088–3099.
72. Roberts I, Shakur H, Coats T et al: The CRASH-2 trial: A randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. Health Technol Assess 2013;17(10):1–79.
73. Dickneite G, Dörr B, Kaspereit F et al: Prothrombin complex concentrate versus recombinant factor VIIa for reversal of hemodilutional coagulopathy in a porcine trauma model. J Trauma 2010;68(5):1151–1157.
74. O'Reilly D, Mahendran K, West A et al: Opportunities for improvement in the management of patients who die from haemorrhage after trauma. Br J Surg 2013;100(6):749–755.

Received: October 25, 2013
Accepted: January 19, 2014