Damage control resuscitation: addressing trauma-induced coagulopathy

Damage control resuscitation attempts early, aggressive correction of trauma-induced coagulopathy in conjunction with interventions designed to achieve early surgical haemostasis and control of contamination. This article reviews the basis of damage control resuscitation and looks at implications for optimizing prognosis after trauma.

Discussions of damage control surgery usually centre on the type and timing of surgical procedures (Moore, 1996; Rotondo and Zonies, 1997). Recently, however, the methods of resuscitation themselves have come under increasing scrutiny for patients with exsanguinating haemorrhage at risk of developing the death triad of acidosis, hypothermia and coagulopathy (Hess et al, 2006; Holcomb et al, 2007).

Damage control resuscitation has been popularized by the military (Borgman et al, 2007), and is being evaluated for its applicability in the civilian setting (Duchesne et al, 2008a). It differs from current resuscitation models by attempting earlier and more aggressive correction of trauma-induced coagulopathy in conjunction with interventions designed to achieve early surgical haemostasis and control of contamination. The concept centres around the finding that trauma-induced coagulopathy is present very early after injury, and earlier interventions to correct it in the most severely injured patients may improve outcomes. In damage control resuscitation the systolic blood pressure is maintained around 90 mmHg, and crystalloid use is limited or non-existent as blood products are transfused at a fixed ratio of one unit of fresh frozen plasma (FFP) for every unit of packed red blood cells (Holcomb et al, 2007). This aggressive resuscitation strategy begins in the emergency room, and continues through the operating room and into the intensive care unit, until haemorrhage is controlled.

Understanding the physiological sequel of exsanguinating haemorrhage and the complex interaction of hypothermia, acidosis and trauma-induced coagulopathy is central to appreciating the potential benefits of damage control resuscitation. As with any new therapy, there is some controversy regarding its efficacy, impact on outcomes, and the evidence for its components (Kashuk et al, 2008; Scalea et al, 2008). This review examines the basis and state of damage control resuscitation, and addresses some implications of damage control resuscitation for the future of resuscitation and optimizing prognosis after trauma.

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Damage control resuscitation

Although damage control resuscitation applies to only a very small subset of the trauma population, its use helps manage trauma-induced coagulopathy through the early and aggressive administration of blood products to the severely injured trauma victim. In a review of combat-related mortality (Holcomb et al, 2007), it was found that the majority of combat deaths are not preventable, while the majority of trauma can be managed with standard resuscitation techniques (Soreide and Deakin, 2005; Borgman et al, 2007; Holcomb et al, 2007). However, most potentially preventable deaths in trauma are caused by truncal haemorrhage and shock (Kelly et al, 2008), making damage control resuscitation an appropriate approach for severely injured patients.

Early and sustained administration of FFP with limited use of crystalloid solution in patients with severe haemorrhage likely helps to correct the state of depleted coagulation factors common in the bleeding patient. A unit of FFP contains approximately 0.5 g of fibrinogen and all the pro- and anticoagulant proteins of blood (Ketchum et al, 2006). Early use of FFP will help replace most of the components of coagulation which trauma consumes or inactivates, while minimizing crystalloid use will limit iatrogenic dilution. While appealing in its simplicity, it is unclear if this accounts for the significant differences seen in existing retrospective studies.

From lessons learned after World War I, intravenous fluids have remained a mainstay of resuscitative therapy (Soreide and Deakin, 2005). In 1985, Hewson et al's retrospective review of 68 massively transfused patients found that coagulopathy was common after crystalloid administration and that an increase in partial thromboplastin time correlated with the volume of crystalloids given. They recommended that FFP and packed red blood cells (PRBC) be given at a ratio of 1:1. For nearly two decades, this recommendation was largely ignored. While describing the effect of fluids on coagulation, Hirshberg and colleagues (2003) concluded that to avoid coagulopathy, PRBCs and FFP must be given in a 3:2 ratio. Ho et al (2005) made similar recommendations.

Current thinking on blood product replacement in severe traumatic haemorrhage has shifted dramatically toward use of a 1:1 FFP to PRBC ratio, largely as a result of evidence from the military's experience with the management of combat casualties. Borgman et al (2007) compared mortality rates associated with varying ratios of FFP to PRBC in the management of trauma seen in Iraq. They found that patients receiving a 'high' ratio of FFP to PRBC (1:1.4) had the lowest overall mortality rates and haemorrhage mortality rates, and concluded that high FFP to PRBC ratio is independently associated with improved survival to hospital discharge, primarily by decreasing death from haemorrhage. Duchesne et al (2008a) found similar results in a civilian trauma centre. From 2746 patients who underwent surgical intervention 626 (22.8%) received ≤10 units of PRBC and 135 (4.9%) received >10 units of PRBC. In univariate analysis, a significant difference in mortality was found in patients who received >10 units of PRBC (26% *vs* 87.5%) when FFP: PRBC was 1:1 *vs* 1:4 (P=0.0001). Multivariate analysis of patients who received >10 units of PRBC showed a FFP: PRBC of 1:4 was consistent with an increased risk of mortality (relative risk = 18.88; 95% confidence interval = 6.32–56.36; P=0.001), compared to a ratio of 1:1. Patients who received ≤10 units of PRBC had a trend toward increased mortality (21.2% *vs* 11.8%) when the FFP: PRBC ratio was 1:4 *vs* 1:1 (P=0.06).

In previous years, hospital massive protocols included a conservative ratio of FFP to PRBCs, often only transfusing FFP after the prothrombin time and partial thromboplastin time became significantly prolonged or after a fixed number of PRBCs were transfused (Borgman et al, 2007; Gonzalez et al, 2007). However, others have argued for a more aggressive approach. Since coagulation factors become depleted quickly in trauma patients with severe haemorrhage, early initiation of haemostatic resuscitation with a 1:1 transfusion strategy helps resuscitation efforts stay ahead of coagulation defects (Ho et al, 2005a).

As clinical experience grows and retrospective data are published, the damage control resuscitation approach is becoming widely used in many trauma centres.

Resuscitation with blood

Fresh whole blood was historically used in transfusion until it fell out of favour in the middle of the 20th century because of infectious disease concerns and the economic benefits of component therapy. There were no clinical efficacy studies comparing component therapy to whole blood in trauma patients. By the late 1980s, component therapy had almost completely replaced whole blood therapy (Kreimeier et al, 2002). Yet over the last 10–15 years, military accounts of the use of fresh whole blood have emerged, noting its usefulness when component therapy was unavailable or when logistically it was the most feasible option. During the battle of Mogadishu, 120 units of fresh whole blood were drawn and 80 units were administered (Sebesta, 2006). Fresh whole blood was also the main blood product when platelets were depleted during the first Gulf War and when profoundly coagulopathic casualties presented in Bosnia and Kosovo (Kauvar et al, 2006). Fresh whole blood is an integral part of the currently US military doctrine and >6000 units have been transfused in the current Gulf war.

Fresh whole blood is such an effective form of transfusion because it replaces all the blood components lost to trauma, including platelets and fully functional clotting factors, and components of fresh whole blood are more viable than their stored counterparts. Separating blood into components results in loss of about half of the viable platelets, PRBCs and clotting factors (Sebesta, 2006) and compromises the integrity and flow characteristics of PRBCs as a result of metabolic depletion and membrane loss (Kauvar et al, 2006). Fresh whole blood skips the steps of separation and storage, allowing better haemostasis (a single unit of fresh whole blood has a haemostatic effect similar to ten units of platelets) (Mohr et al, 1988). Logistically, fresh whole blood has the advantage of being readily available and requiring no delay for thawing. In a forward deployed military hospital in Iraq, transfusion with fresh whole blood resulted in significant improvements in both haemoglobin concentration (9.0–10.7 g/dl) and coagulation parameters (international normalized ratio = 2.0–1.6) (Kauvar et al, 2006).

Transfusion with fresh whole blood or component therapy is associated with risks which should be weighed when deciding whether or not to transfuse a patient. That transfusion is associated with increased mortality, even when controlled for other risk factors, has been well documented (Moore et al, 1997; Holcomb et al, 2007). Transfusion-related acute lung injury occurs in 1 in every 100 000 transfusions commonly 6 hours after transfusion. Although transfusion-related acute lung injury can be a life-threatening antibody-mediated event (Silliman et al, 2005), it usually resolves without adverse outcomes in trauma patients.

Another complication associated with injury and transfusion is multiple system organ failure as a result of immunogenic transfused cells or infection (Moore et al, 2004). Claridge et al (2002) showed that transfused patients were at four times higher risk of developing an infection than those who did not receive transfusion. There is considerable debate about whether these differences are a result of the adverse effects of transfusion or because transfusing the blood products allows patients to live long enough to experience these complications. Some maintain that the increased mortality, time spent in the intensive care unit, and length of hospital stays associated with blood product administration is evidence enough to implicate transfusion products (Malone et al, 2003), while others note that separating the effects of injury from the transfusion has not been proven. At the very least, the picture is unclear (Moore et al, 1997, 2004; Claridge et al, 2002; Malone et al, 2003; Silliman et al, 2005; Spahn and Rossaint, 2005). Data from randomized prospective trials are urgently needed to give definitive conclusions.

Resuscitation with plasma

Early and sustained administration of FFP likely helps to correct the state of depleted coagulation factors common to the bleeding patient. Thus, a key element of haemostatic resuscitation is early and aggressive administration of a 1:1 ratio of FFP to PRBCs. However, there are logistical obstacles to providing FFP as rapidly as it is needed. By definition, FFP is plasma that is frozen at -18°C within 8 hours of being drawn from the donor, so all coagulation factors are preserved at their in-vivo activity levels and remain stable during prolonged storage. Unfortunately, thawing FFP takes 20–30 minutes (sometimes longer), so it is not always available to a massively haemorrhaging patient during the crucial first minutes of damage control resuscitation.

Alternative plasma products, e.g. thawed plasma and liquid plasma, are stored in liquid form, and can be provided to a trauma patient immediately. Some loss of clotting factors occurs when plasma is stored in liquid form, particularly loss of the 'labile' factors V and VIII. Therefore, thawed plasma and liquid plasma cannot replenish clotting factors quite as effectively as FFP. From a practical standpoint, however, plasma products that are stored in liquid form can provide very beneficial replacement of clotting factors during immediate resuscitation.

Thawed plasma can be considered equivalent to FFP. It is stored in liquid form for a maximum of 5 days after it is thawed. At the end of 5 days, coagulation factors other than factors V and VIII maintain 70–80% of their original activity levels, and the fibrinogen level is unchanged. The levels of factors V and VIII are reduced to about 65% activity, but this is well within the haemostatic range (Downes et al, 2001).

With a 5-day shelf life, it theoretically can be difficult to keep an adequate supply of thawed plasma on hand, particularly plasma of the scarce 'universal donor' type AB. However, busy trauma centres have found their waste of plasma has actually decreased by using thawed plasma. Any hospital that uses plasma on a routine basis will likely not waste plasma by keeping 2–4 units available for the rapidly bleeding patient.

Another option is liquid plasma, which has a shelf life of 26 or 40 days, depending on the preservative used. Here, the loss of factor V and VIII activity becomes more significant. At 26 days, fibrinogen and most coagulation factor levels are virtually unchanged. Factor V has approximately 35% of its original activity at 26 days, which is still within the haemostatic range. Factor VIII activity declines to about 10% at 10 days (Smak Greggor et al, 1993). Of note, factor VIII is an acute phase reactant generated by the patient which can also be provided in cryoprecipitate infusions. A reasonable policy in a busy trauma centre would be to keep 2–4 units of type AB or A thawed plasma or liquid plasma available for the initial damage control resuscitation. Thawed, type-specific FFP can be provided once the patient's blood type has been determined and the FFP has been thawed.

Resuscitation with platelets

While most proponents of damage control resuscitation agree on the need for early administration of FFP, there is still debate about the need for platelets. Several studies on blood product ratios use 1:1:1 FFP to PRBC to platelets (Malone et al, 2003; Ho et al, 2005b; Kauvar et al, 2006; Holcomb et al, 2008). The rationale is simple: platelets are easy to administer, do not require thawing, and produce a readily measurable effect on coagulation by immediately increasing the absolute platelet count (Ho et al, 2005a).

Holcomb et al (2008) reported improved survival by transfusing earlier and increased amounts of platelets, but there are problems with the efficacy of platelet administration. Platelets lose a degree of functionality when stored (Spahn and Rossaint, 2005) via a decrease in expression of high affinity thrombin receptors (Tieu et al, 2007), and although absolute platelet count is readily measured, there is no way of knowing how many native or transfused platelets are restored to full functionality (Ketchum et al, 2006; Schreiber et al, 2007). Recent data suggest that a close ratio of 1:1:1 of FFP to PRBC to platelets during early haemostatic resuscitation in patients with trauma-induced coagulopathy might have no survival benefit over a 1:1 FFP to PRBC ratio (Duchesne et al, 2009). Prospective multi-institutional studies of platelets' qualitative function and clot strength during early haemostatic resuscitation will help delineate the true impact of platelets in patients with trauma-induced coagulopathy *vs* patients with consumption coagulopathy after severe haemorrhage.

Chemical haemostasis

Newer developments include the discovery and use of coagulation factor VIIa. Recombinant factor VIIa (rFVIIa) has been used to treat patients with haemophilia as well as other congenital and acquired coagulopathies. In patients with active haemorrhage and clinical coagulopathy from diverse causes such as traumatic haemorrhage, traumatic brain injury, warfarin use, congenital factor VII deficiency and other acquired haematological defects, administration of rFVIIa reversed the coagulopathy in 75% of patients, documented by a decrease in the prothrombin time.

Two randomized prospective placebo-controlled, double-blind trials were conducted to evaluate the efficacy and safety of rFVIIa as adjunctive therapy for the control of bleeding in patients with severe blunt (n=143) or penetrating (n=134) trauma. In blunt trauma, the need for red blood cell transfusion was significantly reduced by 2.6 units (P=0.02), and the need for massive transfusion (>20 units of packed red blood cells) was reduced (14% *vs* 33%, P=0.03). In patients with penetrating trauma, trends were similar but not significant (reduction in red cell transfusion of 1.0 unit, P =0.10; massive transfusion 7% *vs* 19%, P=0.08). Trends toward reduction in mortality and critical complications were also seen (Boffard et al, 2005). Further studies are needed to evaluate the efficacy, safety and cost-effectiveness of rFVIIa in the management of trauma patients (Duchesne et al, 2008b).

Interest has emerged in use of antifibrinolytics agents in patients with trauma-induced coagulopathy. Tranexamic acid, often prescribed for excessive bleeding, is an antifibrinolytic that competitively inhibits activation of plasminogen to plasmin (responsible for fibrin degradation). It is widely used in patients undergoing coronary artery bypass to minimize autologous blood loss; it has roughly eight times the antifibrinolytic activity of an older analogue, ε-aminocaproic acid. Studies of its benefits in patients with trauma-induced coagulopathy are still needed.

Conclusions

Damage control resuscitation is a new way of approaching the age-old problem of haemorrhagic shock – the leading cause of early deaths in trauma patients. Together with damage control surgery, it allows the trauma surgeon and all who care for these patients to restore intravascular volume while correcting the lethal triad, particularly those with trauma-induced coagulopathy. There are multiple opportunities for investigation that can lead to improved patient outcomes. Prospective randomized studies are needed to see if the assumptions behind the damage control resuscitation concept are valid. **BJHM**

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KEY POINTS

- Damage control surgery usually centres on the type and timing of surgical procedures.
- Understanding the physiological sequel of exsanguinating haemorrhage and the complex interaction of hypothermia, acidosis and trauma-induced coagulopathy is central to an appreciation of the potential benefits of damage control resuscitation.
- Damage control resuscitation helps manage trauma-induced coagulopathy by early, aggressive administration of blood products to the severely injured trauma victim.
- Current thinking on blood product replacement in severe traumatic haemorrhage has shifted dramatically towards use of a 1:1 fresh frozen plasma to packed red blood cells ratio, largely as a result of evidence from military experience with the management of combat casualties and recent experience in civilian trauma centres.
- Damage control resuscitation and damage control surgery allow the trauma surgeon and all who care for these patients to restore intravascular volume while correcting the lethal triad, particularly in those with trauma-induced coagulopathy.