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Review

Damage control resuscitation

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HIGHLIGHTS

- Damage control resuscitation involves hemorrhage control, careful use of crystalloids, and early delivery of high ratios of FFP to RBCs.
- Tranexamic acid (TXA) acts as an anti-fibrinolytic and should be strongly considered in patients requiring massive transfusion.
- Prehospital permissive hypotension should be considered for alert trauma patients with a palpable radial pulse.

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1. Introduction to damage control resuscitation

The pattern of deaths after traumatic injury has been extensively described, first with a classic description of a 'trimodal' distribution of deaths in a landmark 1983 study by Trunkey. However, there have been studies since that time that have noted a more bimodal distribution of deaths, with one in 2005 demonstrating that 50% occurred within the first hour of trauma, 18% between one and 6 h post-injury, and then only 7.6% after one week [1]. Given these findings, the initial management of trauma patients has evolved in order to address this early peak in post-injury deaths. While the concept of surgical 'damage control' has existed as a surgical approach to injury for the past two decades [2], this has now been expanded to the early medical management of traumatic patients. This approach to care has been termed 'damage control resuscitation' (DCR) [3,4]. The American College of Surgeons Trauma Quality Improvement Program (ACS-TQIP) describes DCR as the following: "(1) rapid recognition of trauma-induced coagulopathy and shock; (2) permissive hypotension; (3) rapid surgical control of bleeding; (4) prevention/treatment of hypothermia, acidosis, and hypocalcemia; (5) avoidance of hemodilution by minimizing use of crystalloid intravenous fluid; (6) transfusion of red blood cells (RBC):plasma:platelets in a high unit ratio (>1:2) or reconstituted whole blood in a 1:1:1 unit ratio; (7) early and appropriate use of coagulation factor concentrates; and (8) use of fresh RBCs and whole blood when available." [4].

Early recognition of at-risk patients is key to the appropriate application of DCR principles, in order to avoid the onset of the 'lethal triad' of coagulopathy, hypothermia and acidosis. While hypothermia can be addressed through creating a warm environment and using methods of both passive and active rewarming, the prevention and treatment of acidosis and coagulopathy is more difficult and multifaceted. Fluid management and blood product transfusion strategies continue to be refined based upon evolving literature, but are focused on the minimization of crystalloid use and the balanced administration of all blood components. The final step of DCR is the definitive control of any ongoing bleeding, whether through angiography, operative procedures including damage control laparotomy, or other interventions. This chapter will focus on several key elements of DCR.

2. Resuscitation with blood products

The initial literature regarding the ratios of plasma and RBC transfusion on trauma outcomes came from military reviews of massive transfusion. One such study of 246 patients in a US Army combat support hospital receiving 10 or more units of RBCs during massive transfusion demonstrated that high ratio of FFP to RBC (1:1.4) transfusion was associated with lower overall mortality and lower hemorrhage-related mortality rates, and that plasma to RBC ratio was independently associated with survival [5]. This led to the initial use of the term 'damage control resuscitation' in multiple

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manuscripts, adoption of the term by United States military investigators, and further investigations into the ratio of blood product transfusion in trauma patients [6,7]. A subsequent analysis of 713 civilian patients in the German trauma registry also demonstrated lower 6 h, 24 h, and 30 day mortality rates in patients with higher FFP:RBC transfusion ratios [8]. In addition, a 2008 study in the United States also demonstrated lower risk of mortality after massive transfusion with a ratio of FFP to RBC that was equal to or greater than 1 to 1.5 [9]. Notably, the risk of Acute Respiratory Distress Syndrome (ARDS) was significantly higher in surviving patients undergoing high ratio transfusion, and further studies from this group in patients with hemorrhage undergoing transfusion again showed higher multiorgan failure (MOF) and ARDS rates with FFP transfusion [10]. This raises the concern that while hemorrhage related outcomes are improved, this may be achieved with subsequent development of significant complications requiring intensive management. The results of these studies should be interpreted with the caveat that due to the time periods analyzed, survival bias could be influencing results. The concern is whether the results are due to the intervention or just that patients survived long enough to receive it. A study of 134 patients attempted to address this by factoring in the timing of transfusion into the analysis of blood product ratio, and found no statistical significance in survival between ratio groups, prompting a call for larger prospective trials to address the question of transfusion ratio while accounting for the time of transfusion [11].

Subsequently, several large prospective studies were completed. The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) study was a prospective cohort study analyzing the relationship between the ratio and timing of transfusion and mortality in adult trauma patients who required at least three units of blood during resuscitation [12]. This study demonstrated that the time to transfusion of plasma and platelets was variable across the analysis cohort, and showed that higher ratios of both plasma and platelets to RBCs was associated with decreased 6 h mortality, at which time the majority of hemorrhage related deaths had occurred. This was then followed by the Pragmatic, Randomized Optimal Platelet and Plasma Rations (PROPPR) trial which demonstrated higher rates of hemostasis and lower bleeding related mortality by 24 h in patients transfused with a 1:1:1 ratio of plasma, platelets, and red blood cells, compared to a 1:1:2 ratio [13]. These studies suggest that higher transfusion ratios, ideally 1:1:1 ratios, should be a goal in early resuscitation in order to decrease the mortality from hemorrhage during this time period. While there were no differences in rates of ARDS, MOF, or any of the analyzed complications at 30 days between the treatment groups in the PROPPR trial, the overall rates of MOF and ARDS were high in both groups. These trials did address the concern for survival bias from prior studies by discussing earlier timepoints during the resuscitation process and targeting early transfusion, though it should be noted that the Federal Drug Administration (FDA) only allowed primary end points of 24 h and 30 days.

The role of prehospital transfusion is currently an area of continued investigation. Most recently, a 2015 study of 1677 severely injured patients demonstrated decreased transfusion requirements at 6 and 24 h, and a trend towards lower 6 h mortality in all patients. The subset of patients deemed most likely to benefit from early blood transfusion were shown to have lower 6 h mortality [14]. Of note, this study used the previously published Assessment of Blood Consumption (ABC) score to provide clear criteria for prehospital transfusion. This scoring system includes penetrating trauma to the trunk, hypotension, tachycardia, and positive Focused Assessment with Sonography in Trauma (FAST) exam as predictors of need for transfusion [15]. Multiple randomized trials have now been funded by the Department of Defense to investigate the use of prehospital plasma, in order to determine efficacy and to provide additional guidelines as this practice becomes more widespread [16–18].

3. Use of tranexamic acid and recombinant factors

Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine, and acts as an anti-fibrinolytic by inhibiting the activation of plasminogen to plasmin. With prior evidence that use of TXA reduced the need for transfusion in elective surgery [19] both military and civilian groups have studied the utility of TXA in trauma patients. The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH-2) study was a multinational randomized controlled trial of 20,211 adult trauma patients who were assigned to a loading dose followed by infusion of tranexamic acid versus placebo within 8 h of the time of injury. All cause mortality was shown to be lower in those treated with tranexamic acid and also demonstrated lower risk of death due to bleeding, without any difference in the rates of any vascular occlusive event. Further analysis demonstrated that early treatment was particularly important in order to decrease the risk of bleeding-related death, with the most significant reduction seen in those treated within 1 h of injury, though the effect also was seen in those treated between 1 and 3 h after injury. The data also suggested that there may actually be increased risk of death if patients were treated after 3 h [20,21]. The use of TXA in military trauma has also been retrospectively investigated in the MATTERs studies from the United States military. These studies demonstrated that TXA was associated with a survival benefit in patients undergoing transfusion, though transfusion of other factors including factor VII and cryoprecipitate does make interpretation of these studies more complex [22,23].

While these studies suggest that TXA could be effective in trauma resuscitation, recent data does prompt questions regarding its utility. A 2014 retrospective review from Miami showed increased mortality in severely injured trauma patients receiving TXA compared to those who did not receive TXA, however there were multiple limitations to the study which limit the applicability to other patients and trauma centers [24]. A 2015 review publication analyzed the available data on TXA including both large and small scale trials and studies, with the authors concluding that the data does support the use of TXA, particularly in what they term ‘remote damage control resuscitation’ in the prehospital setting, without significant risk of adverse side effects [25]. However, another 2015 study looking at TXA use in 1032 patients with hyperfibrinolysis based upon thromboelastography showed that there was no benefit from TXA use, first showing increased mortality at 24 h, but then no difference in in-hospital mortality rates after logistic regression analysis [26]. Given the complexity of the data available on TXA and some of the limitations of existing studies, there is no consensus to this point on the utility of TXA in trauma resuscitation. However, in the deployed setting, the current United States Army Institute of Surgical Research (USAISR) Joint Theater Trauma System Clinical Practice Guideline on DCR from February 2013 states that early use of TXA should be “considered strongly for any patient requiring blood products in the treatment of combat-related hemorrhage and is most strongly advocated in patients judged likely to require massive transfusion.” [27].

The use of other agents to reverse coagulopathy in trauma patients continues to be under investigation. The CONTROL trial was a phase three randomized clinical trial analyzing the use of recombinant Factor VIIa in trauma resuscitation. In this study, Factor VIIa was used in 573 patients who continued to have bleeding despite damage control resuscitation and operative management. The trial was stopped due to low mortality and enrollment difficulties,