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Management of Exsanguinating Patients in Trauma: a Model for Postpartum Hemorrhage

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INTRODUCTION

Definitive management of the exsanguinating patient challenges providers in multiple specialties. Significant hemorrhage may be encountered in a variety of circumstances including elective or emergent surgical procedures, trauma, gastrointestinal bleeding and major obstetric or postpartum blood loss. Over the past two decades, the vast majority of data and evidence regarding transfusion in the exsanguinating patient has described patients with traumatic injuries. Hemorrhage remains the leading cause of death in the first hour after traumatic injury. It also represents the most frequent potentially preventable cause of early death secondary to trauma[1,2]. The data from such patients can be extrapolated to the treatment of all patients undergoing transfusion for major hemorrhage.

The ultimate goal in the management of exsanguinating patients is to achieve hemostasis and restore circulating blood volume without induction of significant pathologic events such as deep venous thrombosis, cerebrovascular accident, or myocardial infarction[3]. Achieving this goal requires early recognition of the extent of the hemorrhage, control of bleeding which can be accomplished with direct surgical intervention and hemostatic resuscitation with utilization of massive transfusion protocols.

THE LETHAL TRIAD

The 'lethal triad' is presently recognized as playing a major role in the morbidity and mortality of severely injured or bleeding patients[4,5]. Components of the lethal triad consist of hypothermia, acidosis and coagulopathy. This concept was first described by Kashuk and associates in the early 1980s. These authors depicted a 'bloody vicious cycle' in which hemorrhage, cellular shock and tissue injury contribute to the formation of the lethal triad which ultimately resulted in the exacerbation of ongoing hemorrhage[6].

Hypothermia is a common finding in patients with profound blood loss, as patients in hemorrhagic shock have uncoupling of the normal metabolic and thermoregulatory pathways, which results in reduced heat production[7]. The process of resuscitation frequently involves infusion of hypothermic blood and crystalloid, a factor which further contributes to hypothermia[8]. Moreover, patients are often exposed for examination or during surgery and experience ongoing conductive, convective and evaporative heat loss. This is significant, because hypothermia greatly affects platelet activation and the clotting cascade. Indeed, platelet aggregation fails in the majority of patients when the core body temperature falls below 30°C[9]. *Severe hypothermia, defined as a core temperature below 32°C, has been associated with a near 100% mortality in trauma patients with hemorrhagic shock*[10].

The second well-described aspect of the lethal triad is acidosis. By definition hemorrhagic shock results in decreased tissue perfusion. This leads to the build up of the products of anaerobic metabolism, mainly lactic acid. At a lower pH, coagulation is affected by reduced activity of both the intrinsic and extrinsic coagulation pathways as well as alterations in platelet function[11,12]. In addition to a decrease in clot formation, an acidotic state has also been associated with an increase in fibrinolysis in animal models[13].

The third component of the lethal triad is coagulopathy. Multiple factors contribute to coagulopathy in bleeding patients. In addition to the hypothermia and acidosis already discussed, other factors include the consumption of limited clotting factors and fibrinolysis[14–16]. Studies have identified the combination of tissue injury and shock as a primary cause of coagulopathy. Brohi and associates hypothesize that release of activated protein C initiates this coagulopathy after tissue hypoperfusion and have demonstrated that coagulopathy exists very early after injury and before any resuscitative efforts[17–19].

Early recognition of hemorrhagic shock followed by addressing each aspect of the lethal triad is of the utmost importance. Early recognition of significant hemorrhage remains a formidable challenge in obstetrics as hemodynamic changes are often delayed until profound blood loss has already occurred. Therefore,

in all patients hypothermia should be avoided by elevating room temperatures and heat-loss prevention strategies should be instituted. Cold, wet, or damp clothing or bedding in contact with the patient should be removed. Heating blankets, solar blankets and other body heating devices can be used to lessen conductive and evaporative heat loss. Additionally, intravenous fluid should be warmed to body temperature or given through an infuser capable of warming the intravenous fluids prior to administration.

Acidosis, the second part of the lethal triad, is addressed by prevention and treatment of shock. This is achieved by restoring the circulating blood volume and therefore global tissue perfusion. The two most common isotonic fluids used in immediate resuscitation are normal saline (NS) and lactated Ringer's solution (LR). The pH of NS ranges between 4 and 6, while the pH of LR ranges between 5.5 and 7[7]. Resuscitation with NS alone has been shown to contribute to acidosis. This is likely related to the excess chloride in normal saline leading to a hyperchloremic metabolic acidosis. In fact, rapid saline infusion in patients undergoing gynecologic surgery has been shown to produce a hyperchloremic acidosis not seen with LR[20]. Animal models of uncontrolled hemorrhage have demonstrated LR to be superior to NS for resuscitation[21–24]. Animals receiving NS required nearly twice the volume of fluid to achieve and maintain their baseline blood pressure and they experienced increased blood loss[22]. Other adjuncts to treat acidosis, such as bicarbonate, have not been shown to reverse acidosis-induced changes in coagulation and are currently recommended only as a temporary measure in those patients with renal dysfunction in which acidosis clearance or compensation is ineffective[8,25].

Coagulopathy represents the third treatable aspect of the lethal triad. Over the past two decades, research in this area has laid the foundation for the concept of 'hemostatic resuscitation' and has been the focus for management of coagulopathy in the hemorrhaging patient.

HEMOSTATIC RESUSCITATION

Hemostatic resuscitation is a dynamic model which incorporates 'damage control surgery', while emphasizing the *early and aggressive utilization of blood components to correct coagulopathy with massive transfusion protocols*. The term damage control surgery has become synonymous with the management of hemorrhaging patients. This technique emphasizes the principle of life-saving hemorrhage control followed by a period of physiologic correction prior to definitive therapies[26,27]. This requires minimal time spent in the operating room with the major resuscitation occurring in the intensive care unit. Operating room time is minimized by planning staged operations and utilization of temporary dressings (Figure 1). This technique has proven essential in the management of traumatic hemorrhage, and it can be extrapolated to the obstetric patient in two specific scenarios. First, for patients who require operative intervention to manage surgical blood loss, abdominal closure should be delayed. Second, this technique may be required for patients who develop abdominal compartment syndrome as a complication of massive resuscitation and require decompressive laparotomy.

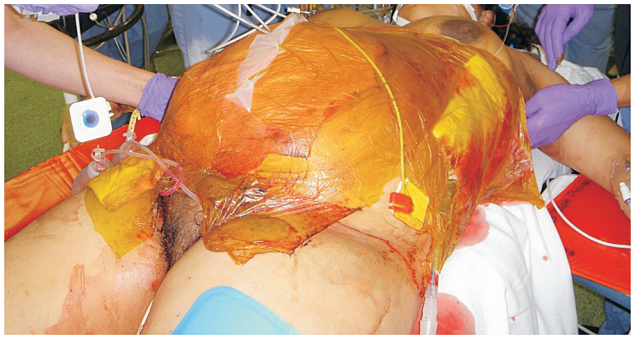

Figure 1 Temporary abdominal closure as part of damage control resuscitation

Definitive control of surgical bleeding involves several techniques including vessel ligation, embolization via an endovascular approach or utilization of pressure and packing for local hemorrhage control. The techniques of vessel ligation, embolization and packing are discussed in detail elsewhere in this textbook (see Chapters 49 and 52–54); however, one additional adjunct to packing includes the use of topical hemostatic agents (see Chapter 58). Advances in biotechnology have led to the development of these agents in the local control of hemorrhage. Examples of topical hemostatic dressings include Quick Clot (Z-Medica, Newington, CT) a zeolite-based dressing and HemCon (HemCon, Inc., Portland, OR) a chitosan-based dressing. QuickClot Combat Gauze (Z-Medica, Newington, CT) is gauze impregnated with the hemostatically active clay kaolin. These agents have proved effective in stopping hemorrhage in animal-based studies[28,29], as well as in civilian and military trauma[30–32]. Combat Gauze is the current dressing that is used by the US military. These agents also have been used for vaginal packing to treat PPH in a patient who required emergency cesarean section (Figure 2). A comprehensive review of the subject has been completed by Achneck and associates and includes an evaluation of efficacy and recent recommendations[33].

Aggressive utilization of blood components during hemostatic resuscitation entails delivery of packed red blood cells (PRBC), fresh frozen plasma (FFP) and platelets in a fixed ratio during a massive transfusion. Massive transfusion in the current literature is defined as transfusion of 10 or more units of PRBC within a 24-hour time period[34–39] (see also Chapter 4). *The ratio of 1 unit of FFP and 1 unit of platelets for each unit of PRBC has evolved over the past two decades.* Support for this concept has come through the development of mathematical models, retrospective studies in both the military and civilian settings as well as through multicenter prospective cohort studies. *The basic concept is closely to re-approximate whole blood utilizing component therapy.*

In 2003, a computer model was developed based on trauma patients receiving a massive transfusion at a major trauma center in the United States. This computer model predicted the optimal ratio of PRBC to FFP was 3 : 2 and the optimal ratio of PRBC to platelets was 10 : 8 in order to prevent early coagulopathy[40]. In 2007, Borgman and associates reviewed 246 military trauma patients who underwent massive transfusion. They divided the patients into three groups based on the ratio of FFP to PRBC transfused. A low ratio of FFP to PRBC was defined as 1 : 8, medium ratio was 1 : 2.5 and a high ratio of FFP to PRBC was defined as 1 : 1.4. The mortality decreased from 65% in the low ratio group to 34% in the medium and 19% in the high ratio group[41]. *Studies in civilian trauma patients yielded similar results and concluded that an FFP to packed red blood cell ratio of 1 : 1 confers a survival advantage in patients undergoing massive transfusion*[42,43].

This concept has been expanded to include the use of platelets. Holcomb and associates reviewed the records of 466 trauma patients undergoing massive transfusion and divided them into groups based on FFP and platelet ratios to PRBC. They demonstrated that when high platelet and high FFP to PRBC ratios are combined there was a decrease in hemorrhage and increase in 6 hour, 24 hour and 30 day survival[44]. An additional multicenter retrospective study reviewed transfusion ratios during the first 6 hours after admission. Compared with a platelet to PRBC ratio of more than 1 : 4 versus 1 : 1, 6 hour mortality decreased from 22.8% to 3.2%[45]. While these studies show strong support for the use of high ratios of FFP and platelets to PRBC, it should be noted that not all studies support improved outcomes[46,47].

Retrospective studies showing a benefit of hemostatic resuscitation are potentially confounded by survival bias. Due to the fact that blood components are not administered in a uniform fashion, enhanced survival rates could be due to the fact that patients who received a higher ratio of FFP to PRBC simply live long enough to receive the FFP transfusions, which take time to prepare. Early massive transfusion is dominated by the use of PRBCs because of immediate availability in most centers. Later in the massive transfusion other products become available. Therefore, patients who die early will have received a low ratio of platelets and plasma to PRBCs.

Snyder and associates analysed 134 trauma patients who underwent massive transfusion. Similar to other studies, they found a 63% lower risk of death for patients who received high ratio (1 : 1.3) compared with patients who received a low ratio (1 : 3.7). However, the survival benefit was no longer seen when they treated the FFP : PRBC ratio as a time-dependent co-variate[35]. *Although controversy in opinions exists, the vast majority of authors agree transfusion of a high ratio of FFP and platelets to PRBCs confers a survival advantage in patients undergoing massive transfusion*[7,34,38,40,41,43,47–55]. *Many trauma centers in the United States presently have adopted a 1 : 1 : 1 ratio of PRBC to FFP to platelets as the standard during a massive transfusion and recommend this as a goal ratio in hemostatic resuscitation*[7,15,38,41,42,49–51,55,56] (Figure 3). The ability to transfuse high ratios is facilitated by maintaining a quantity of thawed plasma at all times. In resource poor environments when component therapy is not available, fresh whole blood is superior to high ratio component therapy[57–59]. In order to effectively achieve the goal of a 1 : 1 : 1 ratio, however, massive transfusion protocols should be in place.

MASSIVE TRANSFUSION PROTOCOLS

Massive transfusion protocols (MTPs) vary considerably from institution to institution and no internationally accepted protocol exists. Nevertheless, they should be considered an integral part of hemostatic resuscitation. The goal of these protocols is to produce an algorithmic, proactive, ratio-based approach to facilitate timely blood product release and mitigate blood bank delays[19,51]. Retrospective analyses have compared the mortality rates for trauma patients requiring massive transfusion before and after implementation of a MTP. In addition to a decrease in mortality, these studies have

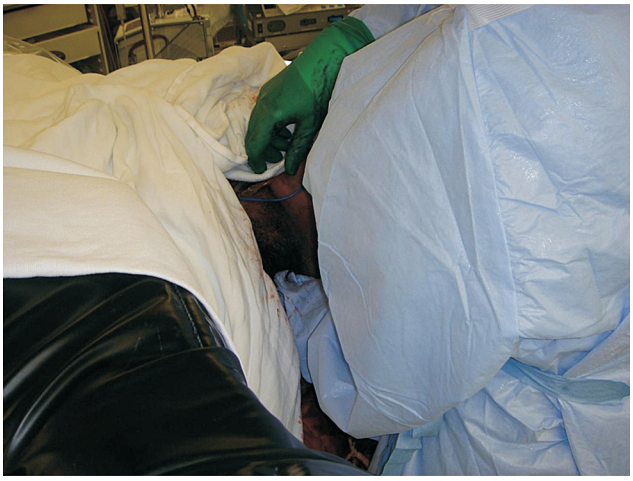

Figure 2 Vaginal packing with Combat Gauze to treat postpartum hemorrhage

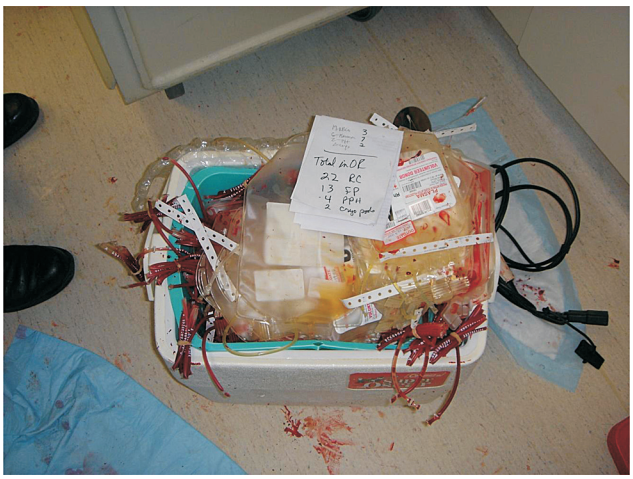

Figure 3 Example of massive transfusion protocol ratios

also demonstrated a decrease usage of crystalloids and an increased FFP : PRBC ratio[60,61].

Cotton and associates developed a trauma exsanguination protocol (TEP) which involved immediate and continued release of blood bank products in a predefined ratio. All TEP activations were retrospectively evaluated with a comparison cohort of patients who received more than 10 units of PRBCs in the 2 year time period prior to TEP initiation at their center. A multivariate analysis was performed which demonstrated a 74% reduction in mortality among patients in the TEP group ($p = 0.001$). Additionally, overall blood product consumption was significantly reduced in the TEP group[62].

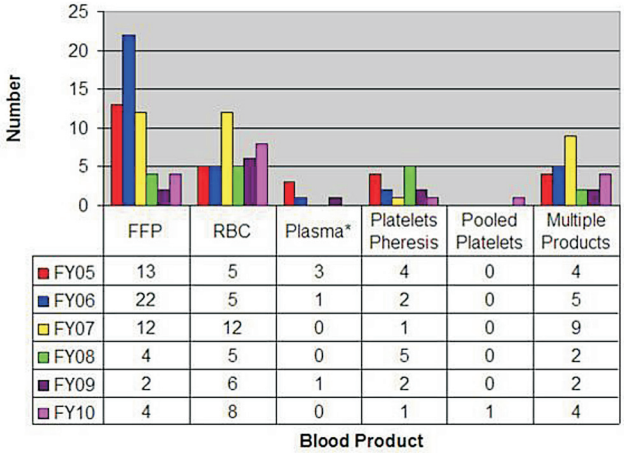

Figure 4 Incidence of transfusion related acute lung injury per blood product given in the US 2005–2010. FY, fiscal year

COMPLICATIONS OF MASSIVE TRANSFUSION

The transfusion of blood in humans is never devoid of the possibility of complications. This statement has always been true but is more important for clinicians to be aware of as traditional transfusion practices change and patients receive higher ratios of FFP and platelets to PRBCs. A comprehensive review of complications associated with massive transfusion was recently completed by Sihler and Napolitano[8]. Acute complications consist of allergic hemolytic and nonhemolytic transfusion reactions, transfusion related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO) and electrolyte derangements such as hypocalcemia, hypokalemia and hyperkalemia. Delayed complications include transfusion-related immunomodulation (TRIM), transfusion-associated graft versus host disease (TA-GVHD), post-transfusion purpura (PTP), microchimerism, alloimmunization and iron overload[63].

Specifically, TRALI has emerged as the leading cause of transfusion-related morbidity and mortality[64,65]. TRALI is defined as acute lung injury (bilateral pulmonary infiltrates, PaO2/FiO2 ratio of 300 mmHg or less and absence of left atrial hypertension) presenting within 6 hours of transfusion and not clearly related to other risk factors for acute lung injury or acute respiratory distress[66]. FFP and platelets have been the most commonly implicated products[45,67–70], and multiple mechanisms have been proposed including the theory of an immune antibody-mediated process[71,72]. Multiparous females are the highest risk donors for TRALI events when using FFP, and many blood banks now only use FFP from male donors[65]. According to the United States Food and Drug Administration (US FDA), since the implementation of this policy, there has been a marked reduction in the incidence of TRALI from FFP and now PRBCs are the leading cause (Figure 4).

TRANSFUSION AFTER MASSIVE RESUSCITATION

Controversies exist as to what the optimal hemoglobin level should be, and different clinicians also vary on what should be the end points of resuscitation. It should be noted, however, that studies continue to demonstrate blood transfusion as an independent risk factor for infection, multiple organ failure, systemic inflammatory response syndrome and mortality. Furthermore, this increase occurs in a dose dependent manner[73–75]. In the well know Canadian transfusion trial (TRICC), younger patients and patients with a lower APACHE score were shown to have a higher mortality when a liberal transfusion strategy (hemoglobin goal of 10–12 g/dl) was followed compared with a restrictive policy (hemoglobin goal >7.0 g/dl)[75]. Subgroup analysis failed to show a benefit of liberal transfusion in patients with cardiovascular disease. Acutely hemorrhaging patients and patients with active coronary ischemia were excluded from this study[76]. Once definitive hemorrhage control is confirmed, unnecessary transfusions should be avoided to lessen the risk of additional adverse consequences.

PRACTICE POINTS

- Identification and treatment of the components of the 'lethal triad' is critical to the management of the exsanguinating patient
- Transfusion of a high ratio of FFP and platelets to PRBCs confers a survival advantage in patients undergoing massive transfusion
- Massive transfusion protocols (MTP) should be considered an integral part of damage control and hemostatic resuscitation
- Once control of hemorrhage has been established, a restrictive policy regarding blood transfusion should be instituted.

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