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Transfusion therapy in hemorrhagic shock

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Abstract

Purpose of review—Bleeding and death from hemorrhage remain a leading cause of morbidity and mortality in the trauma population. Early resuscitation of these gravely injured patients has changed significantly over the past several years. The concept of damage control resuscitation has expanded significantly with the experience of the US military in southwest Asia. This review will focus on this resuscitation strategy of transfusing blood products (red cells, plasma, and platelets) early and often in the exsanguinating patient.

Recent findings—In trauma there are no randomized controlled trials comparing the current damage control hematology concept to more traditional resuscitation methods. But the overwhelming conclusion of the data available support the administration of a high ratio of plasma and platelets to packed red blood cells. Several large retrospective studies have shown ratios close to 1 : 1 will result in higher survival.

Summary—The current evidence supports that the acute coagulopathy of trauma is present in a high percentage of trauma patients. Patients who will require a massive transfusion will have improved outcomes the earlier that this is identified and the earlier that damage control hematology is instituted. Current evidence does not describe the best ratio but the preponderance of the data suggests it should be greater than 2 : 3 plasma-to-packed red blood cells.

Keywords

damage control resuscitation; exsanguinations; hemorrhage; massive transfusion; trauma

Introduction

Trauma is the leading cause of death in the age group of 1–44 years [1]. Hemorrhagic shock and exsanguination are responsible for a large number of these deaths, accounting for more than 80% of deaths in the operating room and nearly 50% of deaths in the first 24 h after injury [2–5]. Fortunately, less than 5% of civilian trauma patient admissions will require a massive transfusion [10 or more units of packed red blood cells (PRBCs) in the first 24 h] [6–8]. More importantly, this group of patients who require massive transfusion accounts for 75% of the blood utilization in busy urban trauma centers [9]. Several authors have demonstrated improved outcomes by using predefined ratios of blood products, early in the care of these severely injured patients [7,10••,11•,12,13•,14,15,16•]. Rapid processing and preparation of such a large amount of blood and blood products in a short period of time

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requires significant planning and prior coordination of personnel and dedicated resources to ensure delivery of these products in an immediate and sustained fashion (Fig. 1).

Acute coagulopathy of trauma shock

Over one-third of injured civilian and military patients have evidence of coagulopathy already present on admission to the trauma center [14,17–20]. Not only do available data suggest that this coagulopathy occurs very early (regardless of resuscitation), it is highly lethal [14,17–21]. In light of these findings, military and civilian researchers have increased their focus on the role of acute coagulopathy of trauma shock (ACoTS) in the early management of the exsanguinating patient. ACoTS is not a simple dilutional coagulopathy that occurs in injured patients but a complex problem with multiple factors whose mechanisms overlap with one another [22]. Whereas multiple contributing factors exist, the key initiator to the process of ACoTS is shock. This process is separate and distinct from disseminated intravascular coagulopathy with its own distinct hemostatic failure. Because of this known early coagulopathy, the current approach to managing the exsanguinating patient involves early implementation of damage control resuscitation (DCR) [6,10••]. DCR is composed of three basic components: permissive hypotension, minimizing crystalloid-based resuscitation strategies and the immediate release and administration of predefined blood products (PRBCs, plasma, and platelets) in ratios similar to that of whole blood.

Patient identification and selection for massive transfusion

Identifying patients who will benefit from DCR (only 3–5% of the injured population) is often challenging, even for experienced trauma physicians at busy level 1 trauma centers [6,7]. Whereas there are currently no uniform activation criteria for such protocols, several groups have developed scoring systems (using a variety of anatomic, physiologic, and laboratory variables) to correctly identify the patient who will likely require a massive transfusion [23–26]. Though each of these scoring systems is quite accurate, the majority of these require laboratory data and injury severity assessment. Given these limitations, Nunez and colleagues [27] developed a scoring system that relies only on data (physiology and mechanism of injury) readily available during the primary survey. The Assessment of Blood Consumption (or ABC) score correctly identifies those individuals who will or will not require massive transfusion approximately 85% of the time (Table 1). It is important to note, however, that each of these scoring systems should be used to augment, not replace, a trauma attending's clinical decision-making.

Products of massive transfusion

Whole blood and blood components are a precious commodity used in the resuscitation of the acutely injured patient. Clinicians need to understand the risks and benefits of the transfusion of each of these components. Allogenic blood transfusion is dependent on the millions of volunteer blood donors which accentuates the precious nature of this product.

Packed red blood cells

Component therapy has been the mainstay of transfusion therapy for the exsanguinating patient. PRBCs are the most utilized of the components in the treatment of trauma patients. Each unit has a shelf life of around 40 days. Unfortunately when given without other products it does not simulate what the trauma patient is losing. It is cold, lacks platelets, coagulation factors, and has a hematocrit of 55% [28].

Whole blood

Primarily a tool of the military, used in combat theaters with the mechanism of a walking blood bank [29]. The US military has fresh whole blood (FWB) extensively in the ongoing conflicts in southwest Asia. In a recent review of the military's experience with the transfusion of over 6000 units of FWB, Spinella [30•] was able to show a favorable risk benefit ratio in the use of FWB. FWB is warm, volume is close to 500 ml, hematocrit is 38–50%, 150–400 K platelets, 100% coagulation activity, and 1500 mg fibrinogen or exactly what the patient is losing [28,31].

Plasma

Fresh frozen plasma (FFP) has been available for transfusion since 1941 and as its name implies is kept in a frozen state at −30°C. Once the 200 ml unit of FFP is thawed in a 37°C water bath, it is available for immediate use. It is acceptable to keep this thawed plasma stored at a temperature of 4°C for up to 24 h and it will maintain its full hemostatic factor content [32–34]. After 24 h, plasma has a predictable rate of decreasing hemostatic factor content. Thawed plasma at 5 days does have adequate hemostatic activity to be used in massive transfusion protocols despite significant degradation in factor VIII activity [32,34]. Of the blood components used, plasma is severely limited in the United States; as of December 2007, 95% of the plasma issued for donation from the American Red Cross was from male donors only [35].

Liquid plasma

Another blood component option which contains essentially the same hemostatic factor content as thawed plasma is liquid plasma [34,36–38]. This form of plasma is separated from whole blood but is kept in the liquid phase as opposed to freezing [36]. It has a shelf life of almost a month and still retains enough hemostatic activity to be utilized in the face of a massive transfusion [34,38].

Platelets

Until the late 1960s platelets were not readily available for blood component therapy [39]. In most centers today the platelets are offered either as single-donor apheresis platelets or random-donor platelets which are pooled from multiple donors. Single-donor platelets are equal in volume and platelet concentration to 4–6 units of random donor platelets. Each will provide an expected rise in the platelets of about 20 000 [40]. Of the blood components platelets will have the shortest shelf life with use required within 5 days.

Adjuncts to massive transfusion

PRBCs, plasma, and platelets are the key components of a massive transfusion protocol, with some centers supplementing with cryoprecipitate replacement [8]. As well, some published protocols supplement their delivery with pharmacological adjuncts such as factor VIIa. Though arguably the most cost-effective and evidence-based adjunct, auto-transfusion/cell saver devices are considerably underutilized in the setting of massive transfusion in trauma.

Recombinant factor VIIa

Initial reports from the Israeli military on their use of recombinant factor VIIa (rfVIIa) in seven severely injured patients in 2001 were quite positive, noting cessation of diffuse bleeding and decreased blood product usage [41]. A recent review of the preclinical and clinical data available for the use of rfVIIa showed the drug to be well tolerated and possibly effective in the treatment of trauma-associated coagulopathy [42]. The US military has

evaluated patients from the joint theater trauma registry and found patients who underwent massive transfusion and received rfVIIa early in their course had decreased 30-day mortality [43]. In a randomized study of exsanguinating patients, Boffard *et al.* [44] noted a reduction in the amount of blood transfused but did not find a mortality benefit. Similarly, Stein and colleagues [45] recently published their experience with 'low-dose' rfVIIa (1.2 mg) in trauma patients with evidence of coagulopathy and noted a significant reduction in prothrombin time and utilization of PRBCs and FFP.

Auto-transfusion

Two decades ago, Timberlake and McSwain [46] and Ozmen *et al.* [47] from Tulane showed that the use of an auto-transfusion device (such as a cell-saver) was well tolerated and effective in patients with intra-abdominal contamination and hemoperitoneum [46,47]. Smith and colleagues [48] recently noted that intraoperative blood salvage is not only well tolerated but that application of such devices is associated with a marked decrease in the use of banked blood. In a randomized controlled trial by Bowley *et al.* [49] there was no difference in the intraoperative blood salvage group compared to controls in regards to postoperative sepsis, survival, coagulopathy, and requirement for clotting factors. Given the proven reduction in the use of the precious commodity of banked blood, we would recommend that those centers with the capability to provide this adjunct 'around-the-clock', strongly consider the use of this valuable tool in the management of the exsanguinating patient.

Damage control resuscitation and the optimal ratios

An increasing number of institutions have demonstrated that a small portion of the trauma population will require a massive amount of blood products in a rapid fashion [21,28,50,51]. In light of this, it is essential that trauma centers have an established mechanism to deliver these products quickly and in the correct amounts to these critically injured patients. Several authors have shown that a trauma exsanguination protocol (TEP) can be successfully implemented and have a significant positive impact on trauma outcomes [10••,12,29,52•]. DCR is a team effort that requires teamwork, communication, and collaboration. The goal is to organize a group of individuals to think and act as a team with a common goal [53,54]. DCR evolved from the damage control surgery paradigm advocated by Stone *et al.* [55] and Rotondo *et al.* [56]. DCR involves the aggressive delivery of blood products which begins prior to any laboratory-defined anemia or coagulopathy [6,57,58]. Damage control hematology defines the process of delivering large amounts of blood products (third component of DCR) in an efficient manner in patients who have been identified as having life-threatening hemorrhage [10••,59,60].

To date, there are no prospective data informing clinicians of the optimal ratio of blood products for the massive transfusion trauma patient. Given the difficulty associated with performing a randomized controlled trial in a group of exsanguinating patients, several authors have attempted to define the optimal transfusion regimen in the absence of such a study design. Hirshberg *et al.* [57] created a computer-based hemodilution model to simulate the exsanguinating patient and found that current resuscitation protocols severely underestimated the need for clotting factor replacement. On the basis of their findings, the authors recommended aiming for a ratio of plasma to red blood cells (RBCs) of 2 : 3 and a ratio of platelets to RBCs of 8 : 10. Ho and colleagues [61,62] developed a mathematical model to simulate ACoTS and recommended the equivalent of whole blood be transfused. This ratio is similar to what has been proposed for DCR by the US military in the exsanguinating combat casualty [6,7,31].

An exhaustive review of the literature demonstrated no class 1 data (and little class 2 evidence) describing the ideal ratio to transfuse to the trauma patient with exsanguinating hemorrhage [7,8,11•,12,15,16•,31,51,63••,64]. On the basis of what was available, however, ratios of at least 2 : 3 for plasma : RBC and 1 : 5 for apheresis platelets : RBC seemed justifiable and were implemented [10••]. One group has found that patients receiving their massive transfusion protocol (plasma: RBC of 2 : 3 or greater and apheresis platelets : RBC of 1 : 5 or greater) have lower 30-day mortality when compared to patients receiving less than the prescribed ratios [13•]. This was similar to what the Denver group found in a retrospective review of 133 patients [65].

The clinical practice described by Beekley [31] advocates transfusing on a 1 : 1 : 1 ratio, essentially trying to recreate the transfusion of whole blood. Duchesne *et al.* [11•] recently evaluated their experience of patients who required a massive transfusion at their urban level 1 trauma center. The authors found that those resuscitated with plasma to RBC ratio of 1 : 1 had a distinct survival advantage over those with a ratio of 1 : 4. Holcomb *et al.* [63••] recently reported their findings from a multicenter, retrospective study of 466 massively transfused civilian trauma patients. The authors demonstrated that patients receiving higher ratios (>1 : 2) of plasma and platelets to RBC had decreased truncal hemorrhage and increased survival at 6 h, 24 h, and at 30 days. In an evaluation of the German Trauma Registry, Maegele and colleagues [64] evaluated outcomes in 713 critically injured patients who received a massive transfusion. They saw the greatest reduction in 24 h and 30-day mortality in the patients who achieved a high ratio of plasma to RBC. Sperry *et al.* [16•] recently evaluated 415 blunt trauma patients within the ‘Glue Grant’ database who received 8 units of RBC in 12 h. The authors demonstrated that in those patients who achieved a ratio of FFP : RBC greater than 1 : 1.5, a significantly lower mortality rate was observed in the first 48 h.

Outcomes of massive transfusion protocols

The TEP described by Cotton *et al.* [10••] has now been in place for over 3 years. After the first year, Cotton *et al.* published a retrospective cohort study of all TEP activations (69 patients) and compared them to a pre-TEP cohort of trauma patients who received massive transfusion (70 patients) [10••]. Given similar injuries, there was a 74% reduction in the odds of mortality in massive transfusion patients with the implementation of the TEP. This same group examined postinjury complications in the 2-year TEP group (125 patients) compared to that of the 2-year pre-TEP cohort (141 patients) [66]. Whereas there was no difference in renal failure or systemic inflammatory response syndrome, the incidence of pneumonia, pulmonary failure, open abdomens, and abdominal compartment syndrome were all lower in TEP patients. In addition, sepsis and multi-organ failure were also lower and there was a significant increase in ventilator-free days in the TEP patients. Consistent with previous findings, patients receiving the protocol had higher survival and received less blood products overall when compared to the nonprotocol cohort [66].

Other authors have also noted a significant benefit to the implementation of a massive transfusion protocol. Duchesne and colleagues [34] evaluated patients before and after establishing a massive transfusion protocol demonstrating more intraoperative blood product usage, high ratio of plasma to PRBC, less crystalloid use, and a significant reduction in mortality with patients receiving the massive transfusion protocol. Similarly, O'Keeffe *et al.* [52•] were able to show decrease in overall blood component usage and cost savings following massive transfusion protocol implementation. However, unlike Duchesne and Cotton they failed to demonstrate an improvement in mortality in the study group [52•].

Those injured in military conflict have also been shown to benefit from a predefined DCR protocol [7,51,67]. Fox *et al.* [51] looked retrospectively at two cohorts with extremity vascular injury from the Joint Trauma Theater Registry [68]. One cohort was prior to the widespread implementation of a clinical practice guideline employing DCR strategies; the other cohort was a group in which DCR was used [51]. This initial case control study showed that combat support hospitals in the combat theater were meeting the goals of DCR and furthermore showed excellent restoration of the patients' normal physiology and excellent early limb salvage [51,67].

Conclusion

Up to 5% of civilian trauma patients will require massive transfusion. This group of patients is likely to be coagulopathic on admission and require transfusion of large amounts of blood products in a relatively short period of time. Massive transfusion protocols are associated with improved survival in patients with exsanguinating hemorrhage. Much of this improvement in survival has been attributed to increased plasma and platelet to RBC ratios. However, our experience (as well as that of recent data) suggests that a well defined protocol with uniform early activation criteria, delivering of products in prespecified ratios and volumes, and a robust performance improvement/quality improvement (PI/QI) process is critical to the observed reductions in mortality. With a team effort, damage control hematology can improve patient outcomes and reduce overall blood product use.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 601–602).

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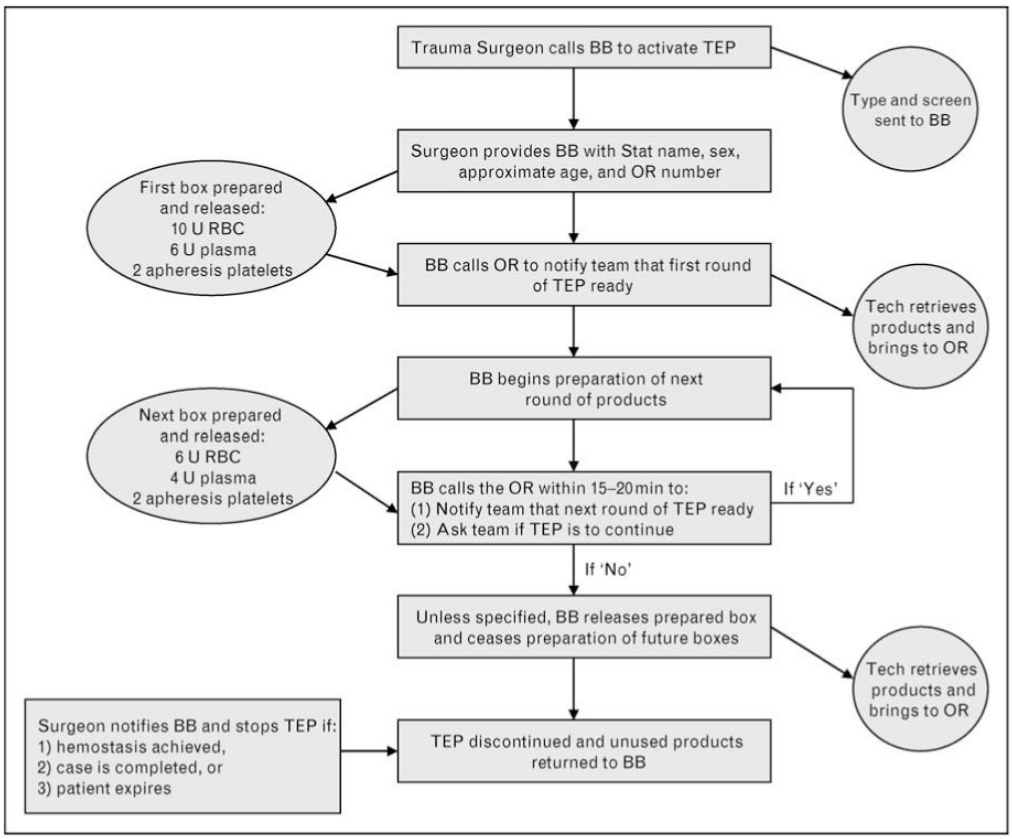

Figure 1.
Proposed algorithm for massive transfusion protocol implementation

Table 1

Suggested nonweighted, nonlaboratory scoring system to predict the need for massive transfusion

Assessment of Blood Consumption (ABC) score
ED systolic blood pressure ≤90mmHg (0 = no, 1 = yes)
ED heart rate ≥120 b.p.m. (0 = no, 1 = yes)
Penetrating mechanism (0 = no, 1 =yes)
Positive fluid on abdominal ultrasound (0 = no, 1 =yes)
Score of 2 predicts 38% need for massive transfusion
Score of 3 predicts 45% need for massive transfusion
Score of 4 predicts 100% need for massive transfusion