Resuscitation and Blood Utilization Guidelines for the Multiply Injured, Multiple Amputee

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Given the current tempo of overseas contingency operations, military orthopaedic surgeons are increasingly performing their duties in an austere environment. At Level 1 trauma centers and combat support hospitals, resources tend to be more abundant than in less "metropolitan" locations. Combat casualty care has reinforced the idea of a multidisciplinary team approach to severely injured trauma patients. During mass casualty situations, as seen recently in Haiti and in the wake of Hurricane Katrina, all members of the trauma team may need to perform duties on the periphery of their comfort zone. Early involvement of orthopaedic surgeons in damage control surgery, as well as resuscitation, are critical to the survival of patients with high amputations, multiple amputations, open pelvic injuries, and mangled extremities common in high-energy penetrating and blast-induced trauma. This article introduces the concept of Damage Control Resuscitation to the orthopaedic surgeon, and also presents a treatment guideline for use as appropriate. (Journal of Surgical Orthopaedic Advances 21(1):15–21, 2012)

Introduction

The battlefields in Iraq and Afghanistan provide a unique opportunity for evaluating combat resuscitation for military surgeons and critical care physicians operating in austere environments. Survival rates are higher than in any previous conflict due to improvements and increased use of personal protective equipment (PPE), tourniquets, far forward surgery, the development of an evacuation system that returns patients to the United States within 3 to 5 days of injury, and the application of Damage Control Resuscitation (DCR) practices (1). Hemorrhage is the number one cause of preventable death among injured combatants (2,3). While PPE has dramatically decreased mortality due to abdominal and thoracic trauma, its use has increased the number of survivors with proximal amputations and severe pelvic injuries (4,5). Orthopaedic surgeons participating in far forward casualty care have become uniquely involved with damage control resuscitation, especially since the patients receiving massive transfusions (MT) are frequently amputees. Working as a multidisciplinary team with the trauma surgeons, orthopaedic surgeons in both austere environments and urban centers must possess more than a working knowledge of current resuscitation practices. This article will provide an overview of the resuscitation literature focused on the lessons learned from these conflicts, as well as provide a practice guideline for orthopaedic surgeons in both military and civilian settings.

Evolution of Damage Control Resuscitation

Massive transfusion (MT) is universally defined as giving 10 U of packed red blood cells (PRBC) over 24 hours. Importantly, patients who receive MT both in military (7%) (6) and civilian (1%–2%) (7) settings have an increased risk of death due to multiple organ failure (MOF), systemic inflammatory response syndrome (SIRS), and sepsis (8,9). Large volume isotonic crystalloid resuscitation, popularized during the Vietnam War and continued today, may significantly contribute to morbidity and mortality in patients receiving MT. Over the last 10 years, multiple studies have documented that crystalloid resuscitation, especially racemic lactated ringers, can cause an increased inflammatory response and organ tissue apoptosis leading to organ dysfunction in animal models (10,11). In addition, clinical studies have revealed an increase in dilutional coagulopathy and abdominal compartment syndrome in critically ill patients undergoing massive crystalloid resuscitation (12–15).

DCR was developed by military trauma surgeons to decrease the harmful effects of massive crystalloid resuscitation and the coagulopathy of trauma. It attempts to reduce coagulopathy by substituting fresh frozen plasma (FFP), platelets (PLT), and cryoprecipitate (cryo) for isotonic crystalloids in early resuscitation (16–19). In a recent retrospective study in combat casualties by Borgman et al., the authors reported a significant decrease in mortality (65% to 19%, $p < 0.001$) in patients undergoing massive transfusion when the ratio of FFP:PRBC increased from 1:8 to 1:1.4 (20). Several other retrospective studies in both civilian and military populations have confirmed the beneficial effects of increased ratios of FFP to PRBC in patients undergoing massive transfusions (Table 1) (20–29). For example, Texeira et al.'s retrospective registry study of 383 MT patients found the risk of death was reduced with increased FFP:RBC ratios (28). Similarly, Zink and colleagues studied 466 massively transfused trauma patients and documented a significantly decreased mortality rate when the FFP:PRBC was = 1:1

TABLE 1 Summary of component therapy ratio studies (20–29,32–34,59)

Study	Design	Size (n)	Findings	Level of Evidence
Borgman 2007	Retrospective Registry	246	Decreased mortality with FFP:RBC 1:8 (65%) vs 1:2.5 (34%) vs 1:1.4 (19%)($p < 0.001$); hemorrhage mortality rates were 92.5%, 78%, and 37%, respectively ($p < 0.001$). FFF:RBC was independently associated with survival (OR 8.6, 95% CI 2.1–35.2)	III
Dirks 2010	Retrospective Registry	253	No effect on MT mortality	III
Duschesne 2008	Retrospective Registry	135	Decreased mortality with FFP:RBC 1:1 (26%) vs 1:4 (87.5%) ($p = 0.0001$)	III
Gunter 2008	Case-control	259	Decreased mortality with FFP:RBC =2:3(41%) vs <2:3 (62%) ($p = 0.008$); Decreased mortality with PLT:RBC =1:5 (38%) vs <1:5 (61%) ($p = 0.001$)	III
Holcomb 2011	Retrospective Registry	643	Improved 24h ($p < 0.001$), 30d ($p < 0.001$) survival with PLT:RBC 1:1	III
Holcomb 2008	Retrospective Registry	466	Improved 30d survival FFP:RBC ratio =1:2 (59.6%) vs FFP:RBC ratio <1:2(40.4%) ($p < 0.01$) Improved 30d survival PLT:RBC ratio =1:2 (59.9%) vs PLT:RBC ratio <1:2(40.1%) ($P < 0.01$)	III
Kashuk 2008	Retrospective Registry	133	no effect on MT mortality	III
Maegele 2008	Retrospective Registry	713	Improved 6h ($p < 0.0001$), 24h ($p < 0.0001$), and 30d survival ($p < 0.001$)	III
Scalea 2008	Cohort	250	No effect on MT mortality for FFP:RBC as a continuous variable (OR 1.49; 95% CI, 0.63–3.53 $p = 0.37$) or 1:1 ratio as a binary variable (OR 0.60; 95% CI, 0.21–1.75; $p = 0.35$)	II
Shaz 2010	Cohort	216	Improved 24h and 30d survival with FFP:RBC =1:2 ($p < 0.01$) and PLT:RBC =1:2 ($p < 0.01$)	II/III
Snyder 2009	Retrospective Registry	134	24h mortality reduction of 63% (RR, 0.37; 95% CI,0.22–0.64) with FFP:RBC 1:1.3 compared to 1:3.7	III
Sperry 2008	Cohort	415	24h mortality decreased when FFP:RBC = 1:1.5 as compared to FFP:RBC < 1:1.5. ($p = 0.012$)	II
Teixeira 2009	Retrospective Registry	383	RR of death 1.90 ($p < 0.01$) when FFP:RBC >1:8 and = 1:3, and 3.46 ($p < 0.01$) when FFP:RBC = 1:8	III
Zink 2009	Retrospective Registry	452	Mortality reduction from 37.3% (<1:4), to 2.0% (=1:1) ($p < 0.001$)	III

Note: RBC, red blood cells; PRBC, packed red blood cells; FFP, fresh frozen plasma; PLT, platelets; u, units; d, day; h, hour.

(37.3% to 2%, $p < 0.001$) (29). In addition, a 2008 multi-center retrospective study by Holcomb et al. found similar results (23). In 466 massively transfused civilian trauma patients, 30-day survival was significantly increased ($p < 0.01$) in high FFP:PRBC ratios (=1:2) as compared to low FFP:PRBC ratios (<1:2). Notably, Holcomb also found that high platelet and plasma to PRBC ratios were consistent with increased 6-hour, 24-hour, and 30-day survival ($p < 0.05$) (23). The addition of cryoprecipitate, which contains fibrinogen, von Willebrand factor, factor VIII, factor XIII and fibronectin, has also been shown to increase survival in retrospective studies as well (16,26,30). In one of the few prospective multicenter cohort studies, Sperry et al. documented a significant decrease in 24-hour mortality when FFP:PRBC was = 1:1.5 (28). Despite the abundant data available on the benefits of increasing FFP:PRBC, there are no prospective randomized studies currently available. Consequently, in a recent multidisciplinary consensus conference sponsored by the National Heart, Lung, and Blood Institute, the evaluation of optimal FFP:PLT:RBC ratios in trauma resuscitation was determined to be one of the four most important areas needing prospective randomized studies (31).

While the evidence for a 1:1:1 ratio of PRBC:FFP:PLT in massively transfused patients is compelling, there are also studies from single institutions that do not demonstrate improved survival. A prospective comparative study conducted by Scalea et al. at Shock Trauma in Baltimore, MD, found no advantage to using FFP:PRBC in a 1:1 ratio in all patients requiring at least one unit of PRBC and one unit of FFP (32). While this study was prospective, it did not differentiate between different ratios of FFP:PRBC as a requirement for inclusion. The two groups were 1:1 or <1:1. This lack of granularity may have masked the benefit by grouping patients who had slightly less than 1:1 with those who had less favorable ratios. Kashuk et al. reached similar conclusions (33). More recently, a registry study performed in Copenhagen by Dirks et al. also did not show a survival benefit to a FFP:PRBC ratio of 1:1 in MT patients (34). Scalea and Dirks' studies had significantly different mechanisms of injury (MOI) (85% blunt for both) than the Borgman study (94% penetrating), and mean ages (43

versus 24 years). Holcomb's patient population was somewhat different than Scalea and Dirks', with mean age of 39 years and a MOI of 65% blunt. It is also likely that blast injury, which is unique to the military, plays some role in these differences as these studies were carried out in civilian injuries. While debate continues on the appropriate ratio for FFP:PRBC:PLT, there is evidence that minimizing the number of PRBC transfused decreases mortality (8). To that end, the concept of hypotensive resuscitation and the use of adjunctive therapies have been adopted in an attempt to decrease transfusion requirements.

Hypotensive Resuscitation

DCR utilizes the concept of hypotensive resuscitation (HR), which has been shown to reduce exposure to blood products and improve survival (Table 2) (35–38). The goal of HR is to keep SBP between 80 and 90 mmHg (or MAP at 50) prior to the surgical control of hemorrhage. In Morrison et al.'s prospective randomized trial, patients in the HR group utilized less PRBC ($p = 0.05$) and overall blood products than the normotensive group ($p = 0.03$) (35). While their study showed a trend towards improved 30-day mortality, there was a significant decrease in 24-hour mortality ($p = 0.03$) (35). By requiring fewer units of PRBC, patients in Morrison's study avoided the adverse effects of PRBC transfusion, which have been shown to be cumulative (8).

Adjuncts to Component Therapy

Recombinant Factor VIIa

Similarly, adjuncts to component therapy have also resulted in the decreased use of PRBC. One of these adjuncts, recombinant FVIIa has been shown to reduce PRBC use by 20% in blunt and penetrating trauma patients and therefore may help conserve scarce resources as well as decrease the cumulative risk associated with multiple transfusions (39,40). In addition, Spinella et al. retrospectively studied 124 military patients and documented that rFVIIa was associated with a decreased 24-hour

TABLE 2   Summary of key studies for hypotensive resuscitation (35,36)

Study	Design	Size (n)	Findings	Level of Evidence
Bickell 1994	Prospective comparison	598	Overall survival 70% vs 62% ($p = 0.04$)	II
Morrison 2011	RCT	90	Less PRBC ($p < 0.05$), FFP ($p < 0.02$) and overall blood products given ($p < 0.03$) decreased 24h mortality ($p < 0.03$).	I

Note: PRBC, packed red blood cells; FFP, fresh frozen plasma; u, units; h, hour.

(7/49 [14%]) and 30-day (26/75 [35%]) mortality (41). However, despite the recent military data, the civilian CONTROL trial, a Cochrane meta-analysis, and other retrospective studies demonstrated no increased survival benefit (42–44). Finally, concerns related to thromboembolic complications have dampened the initial enthusiasm for rFVIIa.

Tranexamic Acid

While rFVIIa has been used in U.S. trauma centers, tranexamic acid (TXA) is perhaps a more controversial therapy currently employed in massive transfusion protocols (MTP) by the military. TXA is an anti-fibrinolytic agent used in an off-label fashion to reduce blood loss and subsequent transfusion requirements in adult reconstructive and other surgeries. Off-label use in trauma patients has recently become part of the U.S. military doctrine. A recent prospective double-blinded randomized controlled multi-center trial (CRASH-2) compared the use of TXA versus placebo in over 20,000 patients. The study documented a significantly reduced risk of all-cause mortality (1,463 (14.5%) versus 1,613 (16%), $p = 0.0035$) and a decreased risk of death due to bleeding (489 (4.9%) versus 574 (5.7%), $p = 0.0077$) (45). The CRASH-2 data also demonstrated that TXA was independently associated with survival when given within 3 hours of injury (45). The recently published Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) study evaluated 896 patients requiring at least one unit of PRBC. The authors demonstrated that MT subset of patients ($n = 231$) who received TXA had a significantly decreased mortality (14.4% versus 28.1%; $p = 0.004$) (46). They were also able to demonstrate that TXA was independently associated with survival (odds ratio, 7.228; 95% CI, 3.016 to 17.322) and that TXA significantly reduced coagulopathy ($p = 0.003$) (46).

Although evidence suggests a survival benefit with rFVIIa and TXA, they are not currently FDA approved for use in trauma patients and both have demonstrated an increased risk of thrombo-embolic events. It is therefore incumbent upon the provider to use judgment when weighing the benefits and risks of rFVIIa and TXA in MT patients (46,47)

Whole blood

During initial combat operations, component therapy and hemostatic adjuncts are often not available in sufficient quantities to resuscitate patients requiring massive transfusions. While civilian trauma centers have reduced or eliminated fresh whole blood (FWB) from their armamentarium in favor of component therapy, the military continues to utilize FWB by necessity. FWB has proven to be a reliable solution for far forward deployed medical units in need of rapidly transfusable blood products. This blood is often obtained from nearby active duty personnel, who constitute a walking blood bank. In a retrospective study conducted by Spinella et al. of 100 patients who received FWB during resuscitation, 96% had improved 24-hour and 30-day survival when compared to patients receiving component therapy alone (88%) ($p < 0.018$) (48). One of the beneficial effects for FWB use is absence of the storage lesion found in PRBC, which has been shown to be associated with multiple organ failure syndrome and mortality in severely injured trauma patients (49–52). Ideally, PRBC should not be administered to critically injured patients after 14 days of storage (51). Due to logistical constraints, the average age of PRBC administered to trauma patients in Spinella's study was 33 days and may account for the differences in mortality between these two groups.

Despite the beneficial effects of FWB, its use is not without risk. FWB is currently not approved by the FDA for numerous reasons, including the inability to rapidly screen for the presence of bacterial and viral agents. These include human immunodeficiency virus (HIV), hepatitis-B, hepatitis-C virus (HCV), and human T-cell lymphotrophic virus (HTLV) (53). However, in a study by Spinella et al., the authors retrospectively compared the risk profile of component therapy to FWB. They found that transfusion reactions for FWB versus component therapy were 2 of 87 (2.3%) versus 12 of 598 (2.0%), ($p = 0.82$) respectively (53). Of 2,831 units transfused in Iraq and Afghanistan, three (0.11%) tested positive for HCV, two (0.07%) for HTLV, and zero for HIV (53). With the development of accurate, FDA-approved rapid screening tests, transfusion with FWB may become a viable alternative to component therapy in civilian trauma centers, especially during mass casualty/disaster events.

Damage Control Protocol Recommendations

Massive transfusion protocols (MTP) have been shown to reduce MOF, abdominal compartment syndrome (ACS), sepsis, blood product utilization, and to improve survival of MT patients (54–56). In a study by Cotton et al., the authors evaluated 94 MT patients who triggered the MTP at their institution, and evaluated mortality and blood product consumption versus 117 pre-MTP MT patients. Their data showed a 74% reduction in the odds of mortality among patients in the MTP group ($p =$

0.001). They also demonstrated a decrease in component use between MTP and pre-MTP patients ($p =$ 0.015) (56).

A multidisciplinary approach is essential to deliver timely and appropriate treatment to critically injured patients (55,57,58). Surgeons, pathologists, blood bank officers, anesthesiologists, ER, and Critical Care physicians must all be trained and drilled on their institution-specific MTP. The first objective to any MTP must be the identification of possible recipients. The risk factors associated with patients who routinely require initiation of Massive Transfusion Protocol (MTP) are listed in Table 3. Initiation of the MTP must include timely communication to the blood bank regarding potential MT patients. Once the patient arrives, there should be standardized "packs" of blood products and adjuncts readily available. The composition should be institution specific in order to utilize scarce resources appropriately and should also be determined by a multidisciplinary team (58). An example of a MTP currently used in military trauma is included in Table 4.

TABLE 3   Risk factors for massive transfusion (16,60,61)

Injury Pattern:
    Displaced pelvic fracture
    Proximal amputation
    Mangled extremity
    Uncontrolled truncal, axillary, neck, or groin bleeding
    Large soft tissue injuries

Clinical Signs:	McLaughlin 2008 (military)	Rainer 2011 (civilian)
systolic blood pressure	<110 mmHg	=90 mmHg
heart rate	>105 bpm	=120 bpm
hematocrit	<32%	—
hemoglobin	—	=10 g/dL
pH	<7.25	—
base deficit	—	>5mmol/L
GCS	—	=8
CT/Fast + for fluid	—	Yes

Note: mmHg, millimeters of mercury; bpm, beats per minute; GCS, Glasgow Coma Scale; CT, computed tomography.

TABLE 4   U. S. military massive transfusion protocol

	Contents
Pack 1	4u PRBC, 4u FFP, +/− 6pk PLT, 10u cryo, +/− rFVIIa, reassess
Pack 2	4u PRBC, 4u FFP, reassess
Pack 3	4u PRBC, 4u FFP, 6pk PLT, 10u cryo, +/− rFVIIa, reassess
Pack 4	4u PRBC, 4u FFP, reassess
Pack 5	4u PRBC, 4u FFP, 6pk PLT, 10u cryo, reassess, Repeat packs 4&5 as necessary

Note: Cryo, cryoprecipitate; PRBC, packed red blood cells; FFP, fresh frozen plasma; u, units; rFVIIa, recombinant factor VIIa.

Conclusion

Until randomized prospective controlled trial data are available, current Level II and III data demonstrate the value of 1:1:1 ratio in a very specific subset of military trauma patients. Both military and civilian orthopaedic surgeons, while historically not on the front lines dealing with early resuscitation of trauma patients, should nonetheless be aware of damage control resuscitation as many may find themselves practicing in austere environments. As an integrated member of the multidisciplinary trauma team, orthopaedic surgeons should be knowledgeable about and be able to help employ DCR.

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