Massive Transfusion for Coagulopathy and Hemorrhagic Shock

SUMMARY

Exsanguination is a leading cause of early death following traumatic injury. Recent studies demonstrate a survival benefit to protocol-driven transfusion strategies that approach a 1:1:1 [packed red blood cell (PRBC), fresh frozen plasma (FFP), and platelet (PLT)] ratio in patients who require replacement of their total blood volume or greater in 24 hours or less. This resuscitation strategy improves patient survival, reduces hospital / intensive care unit (ICU) length of stay, decreases ventilator days, and reduces patient care costs. Recommendations are also provided for correction of coagulopathic hemorrhage.

RECOMMENDATIONS

- **Level 1: None**
- **Level 2**
  - **Administer blood products in a ratio of 1:1:1 (PRBC:FFP:PLT).**
  - **In patients requiring massive transfusion of blood products, minimize crystalloid resuscitation to prevent dilutional coagulopathy.**
  - **Platelet transfusions are indicated in the following situations:**
    - **Neurosurgical procedures or traumatic brain injury (TBI) with PLT count <100,000.**
    - **Surgical / obstetric patients with microvascular bleeding and PLT count <50,000.**
    - **Any surgical patient with PLT count <20,000.**
  - **FFP (10-15 ml/kg) is indicated in the following situations:**
    - **Hemorrhage with elevated PT or PTT (> 1.5 times normal).**
    - **Urgent reversal of warfarin therapy (see "Warfarin Reversal Guideline")**
  - **Cryoprecipitate should be administered in the following situations:**
    - **Hemorrhage with fibrinogen concentrations <100 mg/dL**
    - **Bleeding patients with von Willebrand's disease.**
  - **Tranexamic acid should be considered in patients with significant hemorrhage presenting within 3 hours of injury**
- **Level 3**
  - **Consider the Massive Transfusion Protocol (MTP) in the presence of:**
    - **Systolic blood pressure ≤ 90 mmHg**
    - **Heart rate ≥ 120 beats per minute (bpm)**
    - **Positive focused sonography for trauma (FAST) exam**
    - **pH ≤ 7.24**
  - **Consider MTP implementation if transfusing ≥ 4 units of PRBCs over 1 hour or expected ≥ 10 units over 24 hours (more than one total blood volume).**
  - **Maintain platelet counts above 100,000 during times of active hemorrhage.**
  - **Correct moderate and severe hypothermia (<34^{o}C)**
    - **Place convective-air or aluminum space blankets over the patient.**
    - **Use humidified mechanical ventilator circuits warmed to 41°C.**
    - **Use fluid warmers for the infusion of fluids at 42°C.**
    - **For refractory hypothermia, consider pleural/peritoneal lavage, or arterio-venous rewarming.**
  - **Consider bicarbonate administration when pH < 7.2**

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

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INTRODUCTION

Patient mortality following traumatic injury has decreased over the past 30 years due to improved damage control procedures. Mortality rates continue to be elevated during the first hours following trauma center arrival, however, among patients with uncontrolled hemorrhage (1). This continued high mortality rate is attributable to ongoing hemorrhagic shock as a result of the self-perpetuating triad of coagulopathy, acidosis, and hypothermia (2). Measures to stop this process have long been a part of trauma resuscitation, including hypothermia management, surgical control of ongoing bleeding, and treatment of coagulopathy with blood products.

In the past decade, there has been a progressive trend towards increased use of blood products during trauma resuscitation, including plasma, platelets, and cryoprecipitate, due to the military experience with whole blood resuscitation in soldiers requiring "massive transfusion". Massive transfusion is universally accepted as the replacement of a patient's blood volume, or transfusion of ≥ 10 units of PRBCs, over a 24 hour period (3-9). Similar "damage control resuscitation" is required in approximately 2-5% of civilian trauma. Such early intervention has been demonstrated to translate into a significant improvement in patient outcome (5-9). Damage control resuscitation is designed to treat coagulopathy prior to its clinical manifestation, therefore stopping the self-perpetuating loop of coagulopathic hemorrhage or the "deadly triad".

The strategy of utilizing higher PRBCs:plasma:platelets ratios is not new and has been shown to have modest improvements in patient mortality (4-6). Most recently, there has been significant interest in protocolization of this transfusion process. Studies demonstrate improved patient outcome with implementation of a massive transfusion protocol (MTP) when compared to physician/lab driven resuscitation (4,5,8,9). This improved mortality has been attributed to reduced time to first transfusion of products, thus addressing the fundamental problem of coagulopathy. Riskin et al. have shown that a protocol-driven process improves communication among departments, improves the availability of and reduces delays in obtaining blood products, and improves patient outcome (5). Additionally, improved outcomes can be attributed to reducing the use of uncrossmatched blood which has been shown to be an independent predictor of mortality (10).

Multiple military and civilian trauma studies of massive transfusion protocols suggest that a 1:1:1 ratio of PRBC to FFP and platelets is optimal and associated with the best outcomes (4,5,8,11-16). Holcomb et al. suggested that trying to achieve a 1:1:1 ratio is optimal as this will most closely approximate a 1:2 goal PRBC:FFP given delays in treatment (6). As for platelets, most studies suggest that transfusing platelets at a 1:1 ratio with PRBCs and trying to achieve a platelet count of greater than 100,000/dL is most beneficial in stopping the coagulopathic cycle and increasing clot formation (5,6). There are a few studies addressing the need for cryoprecipitate and some suggest that transfusing with adequate amounts of FFP will obviate the need for cryoprecipitate (Table 1); however, most studies suggest checking fibrinogen levels in patients who continue to demonstrate coagulopathic hemorrhage with maintenance of a level greater than 100 mg/dL (5,11).

FIBRINOGEN CONTENT IN VARIOUS BLOOD PRODUCTS (11)

1 10 unit cryoprecipitate	2500 mg/150 ml
1 unit of FFP	400 mg/250 ml
1 unit of PRBC	<100 mg
1 six pack of platelets	480 mg
1 unit of apheresis platelets	300 mg
1 unit of whole blood	1000 mg

Identifying patients at risk early is a key difference between damage control resuscitation and MTP driven resuscitation. Patients who arrive at the hospital in profound hemorrhagic shock are easy to identify; it is the patients that arrive relatively stable who are more difficult. Nunez et al. reviewed 596 patients in whom 12.4% met MTP criteria. The need for MTP implementation was identifiable using simple non-laboratory values. Patients with SBP ≤ 90 mmHg or less, positive FAST exam, and heart rate ≥ 120 bpm were more likely to need massive transfusion (17). Mc Laughlin identified four independent factors that

were associated with risk for massive transfusion: heart rate > 105 bpm, SBP <110 mmHg, pH < 7.25, and hematocrit < 32% (18). Specific injury patterns that should prompt consideration for implementation of a MTP include liver laceration with hemorrhage, emergent abdominal aortic aneurysm, pelvic fracture with overwhelming blood loss, massive gastrointestinal hemorrhage, and coronary artery bypass grafting.

LITERATURE REVIEW

Massive Transfusion Ratios

Holcomb et al. retrospectively reviewed 466 MTP trauma patients treated from June 2005 to June 2006 at one of 16 Level 1 trauma centers (6). They identified four groups of patients: (1) high plasma and high platelets, (2) high plasma and low platelets, (3) low plasma and high platelets, and (4) low plasma and low platelets. Survival at six hours, 24 hours, and 30 days was recorded. Survival, ICU stay, ventilator free days, and hospital free days were best amongst the high plasma-high platelet group. The best outcomes were in centers with an active MTP in place. Survival was best in patients with plasma to PRBC ratios >1:2 and with platelet ratios of >1:5 (Class II).

O'Keeffe et al. performed a prospective study of patients for two years after MTP implementation compared to patients from the year prior to MTP (4). Improved times to first transfusion were noted. The MTP patients received fewer blood products in the first 24 hours. Most significantly, the evaluation of differences in cost noted a $200,000 savings despite the more frequent use of factor VIIa as a part of their protocol (Class III).

Riskin et al. reviewed their experience two years prior to and post MTP implementation (5). They originally thought they would see a reduction in the ratio of PRBC to plasma, however, the ratios were similar (1:1.8). An increase in survival was noted following MTP implementation. This was attributed to improved communication with the blood bank improving the time to first transfusion of all products. They recommend activation of a MTP for patients with more than four units of PRBCs in one hour or more than 10 units in less than 12 hours. Resuscitation to hemodynamic stability is recommended instead of a particular hemoglobin or hematocrit target (Class III).

Shaz et al. investigated the relationship of plasma:PRBC, PLT:PRBC, and cryoprecipitate:PRBC transfusion ratios to mortality at a civilian Level 1 trauma center (14). This study looked prospectively from 2007 to 2009 at 214 trauma patients who received massive transfusions. High versus low transfusion ratios of FFP, platelets, and cryoprecipitate to PRBCs were associated with improved 30-day survival.

Inaba et al. studied the impact of platelet transfusion in trauma patients undergoing a massive transfusion (15). This study analyzed data from the institutional trauma registry and blood bank databases of a Level I trauma center. 657 trauma patients who received massive transfusion protocols were stratified into a spectrum of four ratios of platelets to PRBCs, lowest to highest. The higher the ratio of platelets to PRBC, the higher the correlated survival at 12 hours and 24 hours after admission, and survival to discharge from the hospital.

Hypothermia

Hypothermia is a frequent pathophysiologic consequence of severe injury and subsequent resuscitation (19). It is estimated that as many as 66% of trauma patients arrive in the emergency department with hypothermia (20). Gregory et al. found that hypothermia developed at some point in 57% of the trauma patients studied, and that temperature loss was most severe in the emergency department setting (21).

Gentilello classified the severity of hypothermia in the trauma patient as mild (36°C to 34°C), moderate (33.9°C to 32°C), and severe (below 28°C) (19). Body temperatures less than 33°C produce a coagulopathy that is functionally equivalent to factor deficiency states seen when coagulation factor concentrations are less than 50% (19). Thrombin generation on platelets is reduced by 25% at 33°C. The average size of aggregates formed by thrombin-activated platelets was decreased by 40% at 33°C and platelet adhesion was reduced by 33% (20). Adverse clinical effects such as cardiac dysrhythmias, reduction in cardiac output, increase in systemic vascular resistance, and a left shift in the oxygen-hemoglobin saturation curve have been described. Mortality rates as high as 100% are seen in patients

with severe hypothermia and severe injury. The most significant effect of hypothermia in trauma is coagulopathic bleeding due to prolonged clotting cascade enzyme reactions, dysfunctional platelets, and fibrinolysis (22,23).

Rewarming Strategies

Rewarming strategies initiated in the emergency department and operating room are aggressively continued in the intensive care unit. Strategies include passive and active external rewarming and active core rewarming.

Passive External Rewarming

Passive external rewarming involves removing blood- or saline-soaked dressings or blankets, increasing ambient room temperature, and decreasing air flow over the patient by keeping the room doors shut.

Active External Rewarming

Active external rewarming devices include fluid/air circulating blankets, aluminum space blankets and overhead radiant warmers. Conductive rewarming with fluid-filled heating blankets placed under the patient is relatively inefficient because of minimal body-blanket contact, estimated to be less than 30%. Convective-air and aluminum space blankets placed over the patient provide greater heat exchange by creating a 43°C microenvironment around the patient, which effectively stops heat loss. Superior warming is achieved when standard cotton blankets are placed over these blankets and the edges secured, although this limits patient access. Head covering is of prime importance; because significant vasoconstriction does not occur in scalp vessels, and as much as 50% of radiant heat loss occurs from the neck up (16). Aluminized caps are effective warmers, but their use is limited in head injured patients with intracranial pressure (ICP) monitors. The effectiveness of overhead radiant warmers is unclear. When aimed directly onto vasoconstricted skin, these warmers may cause inadvertent burns; yet when directed over a blanket, they provide no direct heat exchange to the patient. During laparotomy, it is recommended that covering exposed bowel with moist towels be avoided because it can increase evaporative heat loss by nearly 250% (19). Dry towels or plastic bags are superior.

Core Rewarming

The hypothermic trauma patient requires active core rewarming which may include airway rewarming, heated body cavity lavage, heated intravenous fluids, continuous arteriovenous rewarming (CAVR), and extracorporeal circulatory rewarming. Humidified ventilator circuits can be warmed to 41°C. Heated gastric, bladder, or colonic lavage is relatively ineffective because of the small surface area for heat transfer (19). Peritoneal lavage is generally not feasible in most trauma patients undergoing laparotomy. Rarely, pleural lavage has been used with the placement of two ipsilateral chest tubes enabling continuous flow of heated water.

Use of warmed intravenous fluids is one of the simplest and most effective means of providing heat to the core in patients requiring massive fluid resuscitation. Current fluid warmer technology allows large volumes of warmed fluids to be infused quickly at 42°C, the current standard recommended by the American Association of Blood Bank (24). Blood-warming methods include surface-contact warmers, counter-current warmers, and heated-saline admixture (25). In-line microwave blood-warming technology (in development) has been shown to heat blood safely to 49°C and shows great promise for the future (26).

Cardiopulmonary bypass has limited applicability in trauma patients due to the need for systemic anticoagulation. An alternative is continuous arteriovenous rewarming (CAVR) (27). In CAVR, percutaneously placed 8.5 French femoral arterial and venous catheters, and the patient's blood pressure, create an extracorporeal arteriovenous circuit that uses the heating mechanism of a counter-current fluid warmer. Early studies have shown the greater effectiveness of CAVR in comparison with traditional warming techniques in rapidly rewarming trauma patients with severe hypothermia (25). However, widespread use of this device has been limited due to: 1) the learning curve for involved personnel; 2) the infrequency of use at many trauma centers; 3) its negligible effect on long-term survival; and 4) its associated increase in respiratory distress syndrome, length of

hospital stay, and cost. Veno-venous bypass, although more complex than arteriovenous systems, can also be performed by using a conventional roller pump to drive blood through a heat exchanger, however, this requires the constant attention of qualified personnel (29).

Acidosis

The association between high lactate levels and increasing risk of death was first described over 40 years ago by Broader and Weil (30). Since then, several investigators have demonstrated increasing risk of death with metabolic acidosis as demonstrated by arterial pH, lactate, and base deficit clearance (31). The deleterious effects of acidosis on the cardiovascular system include decreased cardiac contractility and cardiac output, vasodilation and hypotension, decreased hepatic and renal blood flow, bradycardia, and increased susceptibility to ventricular dysrhythmias (32). Acidosis directly reduces the activity of the extrinsic and intrinsic coagulation pathways as measured by PT and PTT and also diminishes platelet function as measured by platelet aggregation and platelet factor III release (19). These adverse effects are generally not seen until pH decreases below 7.2 (32).

Therapy for metabolic acidosis remains directed toward correcting the underlying hypoperfusion. Resuscitation endpoints include normalization of arterial pH, base deficit, and lactate. In clinical trials, researchers have failed to demonstrate any clear advantage of bicarbonate administration, whereas the potential adverse effects are well documented (24). Bicarbonate administration should be deferred until the pH persists below 7.2, despite optimal fluid loading and inotropic support (34).

Tranexamic Acid

Tranexamic acid is an antifibrinolytic agent that has historically been shown to decrease the need for blood transfusions in patients undergoing elective surgery. In 2010, a multi-national randomized, double-blind placebo-controlled trial (CRASH-2) analyzing 20,127 trauma patients was published. The trial included patients with significant hemorrhage (systolic blood pressure <90 mmHg or heart rate >110 beats per minute, or both) and if they were within 8 hours of injury. The patients received either 1 g of tranexamic acid over 10 min followed by an intravenous infusion of 1 g over 8 hours or placebo. The tranexamic acid group had a significantly lower all-cause mortality at 28 days than the placebo group [14.5% vs. 16%; relative risk (RR) 0.91, 95% CI 0.85-0.97; p=0.0035] (35).

In 2011, the CRASH-2 investigators published an exploratory analysis of the previous trial that specifically evaluated the effect of tranexamic acid on death due to bleeding subdivided by time from treatment to injury. The results showed that earlier treatment with tranexamic acid is more effective in reducing the risk of death due to bleeding. Patients that received tranexamic acid within 1 hour of injury had a death rate due to bleeding of 5.3% versus 7.7% for placebo (RR 0.79, CI 0.64-0.97; p<0.0001). Similarly, patients that received treatment between 1-3 hours from injury also had a significantly lower risk of death due to bleeding. However, patients receiving tranexamic acid >3 hours from injury had a significantly increased risk of death compared to placebo, 4.4% vs 3.1%, respectively (RR 1.44, CI 1.12-1.84; p=0.004) (36).

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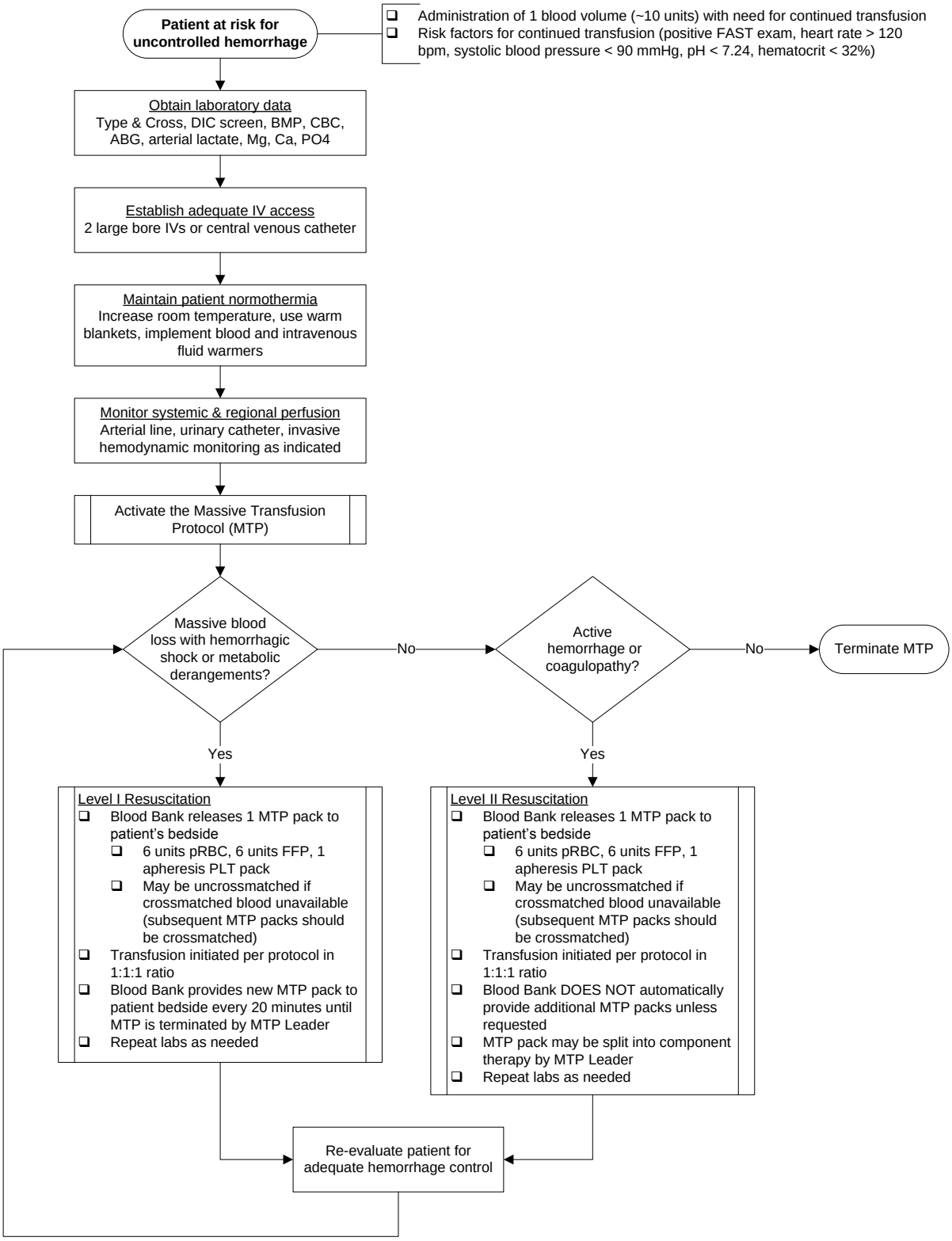
MASSIVE TRANSFUSION PROTOCOL



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