Introductory comments from the COBM chair.

Despite significant advances in trauma management including pre-hospital care, rapid evacuation, fluid management and 'damage control' surgery, mortality from hemorrhagic shock remains the number one cause of death in civilian and military trauma victims.

The complexity of this injury is compounded by alterations in the coagulation system with a tendency towards a hypocoagulable state, although the coagulation systems' response under these conditions is not fully understood, and is skewed by only testing the pro-coagulant arm.
Data from our latest battle fields suggests that reconstituting components of blood to resemble whole blood have better survival profile than conventional component approach or directed therapy. These data are retrospective and as such cannot reliably account for the 'survival effect' where those who survive will receive larger amounts of components at a higher ratio.

Early recognition of associated coagulopathy in trauma patients is essential to improve outcome. Unfortunately, our understanding of trauma related coagulopathy is limited at best, and favors the pro-coagulant deficiency state since most, if not all studies rely on testing this arm.
As we begin the second decade of this century, an enthusiastic call by some of our trauma surgical colleagues to resort to 1:1:1 ratio of major components (RBC, Plasma and Platelets) may be appropriate for some patients, but may put others at risk of worse outcome and possible higher delayed mortality. More convincing data to replace this exuberant enthusiasm is clearly needed. Until these data are available, guidelines for MTP and treatment of the hemorrhaging trauma patient are desperately needed to guide clinicians at the bedside.

The COBM of the ASA has put together a SAMPLE recommendation for such a protocol. We encourage the ASA members to read it and collaborate with their hospital transfusion service and/or blood bank to implement a protocol based on the information provided, adjusted to local needs.

Reference:
Trauma-Induced Coagulopathy – A Review of the Systematic Reviews:
Is There Sufficient Evidence to Guide Clinical Transfusion Practice?
Nicola Curry, Simon Stanworth, Sally Hopewell, Carolyn Doree, Karim Brohi and Chris Hyde.
Transfusion Medicine Reviews, Vol 25, No 3 (July), 2011:pp 217-231

TITLE: MASSIVE TRANSFUSION PROTOCOL (MTP) FOR HEMORRHAGIC SHOCK

ASA COMMITTEE on BLOOD MANAGEMENT

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PRINCIPLE:

A massive transfusion protocol (MTP) is activated by a clinician in response to a patient that is experiencing massive bleeding. The responsible clinician activates the MTP either by phone or any other mechanism. Once a patient is in the protocol, the blood bank is able to insure rapid and timely availability of blood components to facilitate resuscitation.

The need for MTP may be encountered in either surgical or medical emergencies where life-threatening hemorrhage is confronted. Surgical control of hemorrhage (damage control surgery) and timely application of volume resuscitation with fluids and blood components remains the cornerstone of treatment. [i] Once definitive control of bleeding has been achieved, a restrictive approach to blood product transfusion is preferred because of the well-known risks and negative outcomes of transfusion such as multiple organ failure, systemic inflammatory response syndrome, TRALI, increased infection, and increased mortality. [ii], [iii] As examples, the MTPs employed at MetroHealth Medical Center (Cleveland, OH) and University of Kentucky are shown in Tables 1-2.

RATIONALE:

Transfusion of packed red cells (RBCs), plasma, and platelets in a similar proportion as whole blood may minimize the effects of dilutional coagulopathy and hypovolemia.[iv] Remaining controversial, retrospective studies in patients sustaining trauma demonstrate a survival advantage of increased plasma: red cell ratio on mortality in massive transfusion after trauma.[v] (Table 3) Some studies have demonstrated a survival advantage with increased platelet: red cell transfusion ratio. Based on these observations, the optimal ratio of plasma to red cells appears to be in the range 1:2.4 or higher. Because these studies were retrospective, unintended biases may have occurred. For example, more resources, including plasma and/or platelet transfusions, may have been expended on the patients deemed most likely to survive, leading to selection bias. [vi] As well, survivor bias may have occurred, in which surviving patients had more opportunity to receive increased volumes of plasma and/or platelet transfusions, thus potentially leading to higher calculated ratios. Even when the studies in Table 3 recommend 1:1 ratio of components, most do not achieve this ratio. In a survey of members of EAST (Eastern Association for the Surgery of Trauma), 85% of US trauma centers have a MTP.[vii] However, the level of evidence supporting use of a MTP is weak in part since outcome studies in trauma are difficult to perform because modern evidence-based trauma care reduces mortality (e.g., CONTROL trial).[viii] The present data do show that having a MTP has better outcomes than not having one. This is likely because a MTP with increased plasma to red cell ratios allows the physician to intervene early, and use larger doses of plasma. Increasingly, it is recommended that ratio based resuscitation be complimented or replaced with point of care or other laboratory endpoints to better direct therapy. This practice is becoming common in Europe where whole blood clotting testing is available.

DEFINITION of MASSIVE TRANSFUSION: [ii]

The traditional definition of massive transfusion is 20 units RBCs in 24 hours, which corresponds to approximately 1 blood volume in a 70 kg patient. A commonly used definition in the trauma literature is $\geq$ 10 units RBCs in 24 hours. [ix] Both of these definitions are reasonable for publications, but are not practical in an ongoing resuscitation. Other definitions are: loss of 0.5 blood volume within 3 hours; use of 50 units of blood components in 24 hours; use of 6 units RBCs in 12 hours. From a practical standpoint, requirement for > 4 RBC units in 1 hour with ongoing need for transfusion, or blood loss > 150 ml/min with hemodynamic instability and need for transfusion are reasonable definitions in the setting of a MTP situation. The variability in defining massive bleeding

may result in variability initiating a MTP and another reason why having a MTP vs. not may result in early resuscitation and better outcome.

PHYSIOLOGY of HEMORRHAGIC SHOCK in TRAUMA (Figure 1)

Major trauma causes tissue injury and hemorrhage. Shock occurs due to decreased circulating volume, cardiac output and oxygen delivery which is compounded by the associated inflammation, acidosis, and tissue hypoperfusion. Environmental exposure, initial resuscitation with unwarmed fluid and deranged thermoregulation result in hypothermia. Aggressive fluid resuscitation can cause hemodilution with decreased oxygen carrying capacity, decreased oxygen delivery, and dilution of substrate and enzymatic coagulation factors. Progressive coagulopathy leads to further hemorrhage and shock. Refractory coagulopathy, progressive hypothermia and persistent metabolic acidosis lead to end stage shock and death. Prevention and control of coagulopathy is the goal of MTP in the hope of preventing further hemorrhage after trauma.

COAGULOPATHY of HEMORRHAGE and MASSIVE TRANSFUSION in TRAUMA

Patients may have a complex coagulation disorder involving dilution of pro-coagulant, anti-coagulant, pro-fibrinolytic and anti-fibrinolytic factors[x], [xi], [xii] Acute coagulopathy of trauma appears to be due to activation of anticoagulant and fibrinolytic pathways,[xiii] although the exact mechanism has yet to be elucidated. The thrombomodulin–protein C pathway has been implicated. Shock and hypoperfusion are the key drivers of acute coagulopathy of trauma. According to Frith and Brohi,[xiv] hypoperfusion increases the expression of thrombomodulin on endothelium which then complexes with thrombin. This reduces the amount of thrombin available to produce fibrin and increases circulating concentrations of anticoagulant activated protein C. In the obstetric patient, massive bleeding may routinely consume fibrinogen despite available thrombin, hence differences might exist in mechanism of coagulopathy in different patient populations. In trauma, hypothermia and acidosis play a key role by reducing thrombin generation due to altered enzyme kinetics. Both coagulation factors and platelets are reduced by hemodilution. Platelet count is higher than predicted due to release of platelets sequestered in the spleen and lungs. Antithrombin activity decreases to less than 30% of normal with extensive hemodilution. [xv] A hypercoagulable presentation is also possible. With end-stage shock, disseminated intravascular coagulation (DIC) and pathological hypercoagulability may occur. The fibrinolytic pathway is relatively preserved despite hemodilution. Fibrin generation is decreased. A threshold level of fibrinogen 1g/L (100 mg/dL) is reached after losing 150% of circulating blood volume as opposed to 200% for clotting enzymes.[xvi] Systemic hyperfibrinolytic states may be seen in up to 20% of trauma patients.[xvii] Fibrinolysis is significantly increased due to dilution of FXIII and α_2 – antiplasmin which reduces fibrin cross-linking, decreases resistance to fibrinolysis and prolongs plasmin half-life. Plasminogen activator inhibitor is decreased, prolonging tissue plasminogen activator (tPA) activity. Stress, thrombin, epinephrine, vasopressin, desmopressin, and bradykinin trigger tPA release. Excessive fibrinolysis contributes to continued bleeding and possible mortality.

PREDICTING NEED for MTP in TRAUMA:

Approximately 3-5% of civilian adult trauma patients receive massive transfusion.[xviii] Early identification of patients requiring MTP has been evaluated by assigning a value of 0 or 1 to the following four parameters: penetrating mechanism, positive FAST for fluid (focused assessment sonography in trauma), arrival blood pressure <90 mm Hg, and arrival pulse >120 bpm. A score of 2 or more is considered positive. [xix] The score is 75% sensitive and 85% specific. FAST examination identifies whether there is free fluid within the peritoneum, which could indicate organ rupture and internal bleeding. Patients receiving uncross-matched red cells in the emergency department are three times more likely to receive massive transfusion. [xx] In military trauma, casualties presenting with any two of four possible variables (heart rate >110 bpm, systolic blood pressure <110 mm Hg, base deficit $\leq$ -6, and hemoglobin <11 g/dl) had a 54% incidence of massive transfusion.[xxi]

ADJUNCTS TO MTP:

Hypothermia, acidosis, shock, coagulopathy, and failure to control surgical bleeding contribute to mortality after trauma. In addition to a MTP, all efforts must be directed towards damage control resuscitation including control of surgical bleeding and correction of hypothermia, acidosis, shock, and coagulopathy. Implementation of clinical practice guidelines have led to improved survival in trauma.[xxii]

RECOMMENDATIONS for RESUSCITATION in PATIENTS REQUIRING MASSIVE TRANSFUSION AFTER TRAUMA:

Early control of hemorrhage is essential to limit consumptive coagulopathy and thrombocytopenia, and decrease usage of blood. Limiting the use of isotonic crystalloid will help prevent dilutional coagulopathy. Limiting the use of 0.9% saline may prevent further acidosis. Hypotensive resuscitation (systolic blood pressure 80-100 mmHg) until hemorrhage is controlled is generally recommended, unless there is concern for traumatic brain injury. Early use of plasma, platelets as well as RBCs is necessary in an attempt to improve survival with massive transfusion. Fibrinogen levels above 1.5 g/L (150 mg/dL) are targeted.[xxiii] These levels can be achieved with cryoprecipitate 50 mg/kg or fibrinogen concentrate doses of 3-4 g. [xxiii] aboveBase deficit and lactate levels are monitored to assess adequacy of resuscitation in restoring oxygen delivery and tissue perfusion. Electrolyte abnormalities caused by dilution and transfusion should be corrected: hyperkalemia from large volume of banked RBCs, hypocalcemia from citrated anticoagulants, and Na and Cl abnormalities from crystalloid resuscitation. Evidence is growing for use of point of care coagulation testing to guide hemostatic therapy (thromboelastography, thromboelastometry, Sonoclot). [xxiv], [xxv] Standard coagulation tests such as PT, PTT, INR, platelet count, and fibrinogen usually require 30–60 minutes for results to be available. For massive transfusion patients requiring acute interventions, results of standard coagulation tests may not be an accurate reflection of coagulation function. Measurement of platelet count and fibrinogen only provides absolute amounts, not functional activity and may overestimate the levels.

THROMBOELASTOGRAPHY (TEG) and Rotational THROMBOELASTOMETRY (ROTEM):

Two available viscoelastic whole-blood assays measured at 37°C give an in-vitro measure of clotting. These hemostatic assays provide a graph of the displacement caused by viscoelastic changes in whole blood as clotting progresses and fibrin strands form between the cup and pin (Figure 2). Clot strength is decreased by hypofibrinogenemia, thrombocytopenia, low FXIII level, or reduced thrombin generation. Rapid TEG (coagulation is initiated by the addition of tissue factor) gives faster results compared to kaolin TEG. ROTEM, EXTEM (uses recombinant tissue factor to activate coagulation) and FIBTEM (measures contribution of fibrinogen to clot strength) allow differential diagnosis of thrombocytopenia and hypofibrinogenemia. Higher hemoglobin levels reduce TEG/ROTEM signals. Conversely, low hemoglobin makes signals larger.

Application of TEG/ROTEM in Trauma and Acute Hemorrhage (Figure 3)

Kaufman et. Al studied 69 patients with blunt trauma. [xxvi] Sixty-five percent were found to be hypercoagulable at admission and 10% were hypocoagulable. Injury severity (ISS) and

hypocoagulable TEG were predictive of early transfusion. Schreiber et al demonstrated hypercoagulablity in 62% of patients on admission[xxvii] In a study of 161 trauma patients on arrival to the emergency department, [xxviii] clot forming parameters demonstrated hypocoagulability and correlated with mortality. No such correlation was observed with routine clotting tests (PTT INR). Hyperfibrinolysis was identified in the most severely injured patients, and correlated with mortality. [xxix], [xxviii] Kashuk et. al. demonstrated primary fibrinolysis in 34% of patients requiring massive transfusion using TEG. [xxx] Early administration of an anti-fibrinolytic agent (tranexamic acid) to adult trauma patients resulted in reduced all-cause mortality in the treatment group, reduced mortality from bleeding and a safe side effect profile in bleeding trauma patients. [xxxi] It is recognized, however, that severely injured patients who present fibrinolysis have increased mortality, [xi], [xxxii] so the efficacy of tranexamic acid in such patients is questionable. TEG/ ROTEM assays may signal the selection of patients who would most benefit from this intervention.

FACTOR VIIa and MTP in TRAUMA

Two randomized, double blinded, placebo controlled trials with 143 blunt and 134 penetrating trauma patients have been carried out. [xxxiii] The initial dose of rFVIIa was given after the 8th RBC unit and then 1 and 3 hours after (200, 100, 100 mcg/kg). RBC transfusion was significantly reduced in blunt trauma patients, as was the need for massive transfusion (14% vs 33%). There was a trend towards similar results in penetrating trauma which did not reach statistical significance. Subgroup analysis[xxxiv] of coagulopathic patients from both trials showed reduced blood component per patient, fewer massive transfusions (6% vs 29%) and less multi-organ failure and ARDS (3% vs 20%) in the rFVIIa group. Thromboembolic complications were similar to the placebo group. In a study of early vs late administration of rFVIIa (before vs after 8 RBC units) in combat casualties, [xxxv] the early group required less blood (20.6 vs 25.7 units). Mortality, ARDS, infection and thrombotic events were similar between groups. In the CONTROL trial, [viii] rFVIIa decreased RBC, FFP, and total allogeneic blood product use but did not affect mortality. The study was terminated early because of low mortality and there was no difference in arterial and venous thrombotic events in the rFVIIa vs the placebo group. Evidence seems to show benefit for rFVIIa, especially in coagulopathic trauma patients,

however this remains an off- label use and controversial. rFVIIa is not a first-line therapy for hemorrhage. Adequate fibrinogen levels (e.g., > 1.5-2 g/l) and platelet count (e.g., > 50,000- 100,000 x 10^9/l) are necessary for drug efficacy. Control of surgical bleeding and normalizing acid-base status and core temperature are of obvious importance. In a meta-analysis of patients with body trauma, use of rFVIIa reduced ARDS and transfusion requirements, but had no effect on mortality or thromboembolism.[xxxvi] In a review of 35 randomized clinical trials involving 4468 subjects, [xxxvii] the rate of venous thromboembolic events was similar between rFVIIa and placebo treated subjects (approximately 5.3-5.7%). However, arterial thromboembolic events were higher in patients who received rFVIIa vs placebo (2.9% vs 1.1%). The rate of arterial events was highest in patients $\geq$ 65 yrs receiving rFVIIa (9.0%). Because of the risk of serious adverse effects, treatment with rFVIIa must be individualized based on a risk-benefit analysis.

COMPLICATIONS of MTP in TRAUMA

Blood transfusion is an independent predictor of multi-organ failure in a retrospective and prospective study of trauma patients with injury severity score > 15 and survival greater than 24 hours.[iii] There is a 2-6 fold increase in SIRS, 4 fold increase in ICU admission and mortality in transfused patients. One study showed that transfusion was an independent predictor of death in non-operative blunt trauma and the risk of death increased with each additional RBC unit. [xxxviii] In a retrospective review of 1312 patients, the mean transfusion volume for elderly survivors vs young was 4.6 units vs 6.7 units;[iii] No patient over age 75 who was transfused > 12 units RBCs survived. In a meta-analysis of 20 studies, [xxxix] the odds ratio for bacterial infection in transfused vs non-transfused patients was 3.45. The odds ratio increased to 5.26 in the subgroup analysis for trauma patients. All studies achieved statistical significance. Multiple studies have linked transfusion to increased development of and mortality from ARDS. TRALI (lung injury occurring within 6 hours of transfusion) occurs with a 1:5000 incidence in the general transfusion population and is likely increased in massive transfusion, although the extent is unknown. TRALI is likely under-diagnosed after severe injury. It is difficult to differentiate TRALI from transfusion associated circulatory overload or other causes of lung injury in trauma. For non-massively transfused trauma patients, plasma administration is associated with increased complications (ARDS, multiple organ dysfunction, pneumonia, and sepsis) with no improvement in survival[xl] Despite the claim that high ratio MTP reduces dilutional coagulation, some clotting factors do get diluted by the shear volume of components and the limited availability of factors in plasma may not be sufficient to overcome this defect. As such, the early and sometime the sole use of coagulation factors and fibrinogen concentrates is being adopted in European centers. The use of these agents in the US is off label and many are not FDA approved. Firm data on efficacy and safety of this practice is needed and is slowly accruing.

MTP AFTER CONTROL of HEMORRHAGE

A restrictive approach to blood product utilization is advocated once bleeding is stopped and the patient is stable.[iii] . RBC transfusion is generally indicated for hemoglobin < 7 g/dl. For hemoglobin above 7 g/dl, hypovolemia is treated with IV fluids. Signs and symptoms of impaired oxygen delivery and decreased tissue perfusion are closely

monitored. RBC transfusion is generally required for persistent base deficit, lactic acidosis, signs of end organ ischemia, and low mixed venous oxygenation.

MTP in PEDIATRICS

Massive transfusion for pediatric trauma patients generally follow similar principles as in adults.[xli] An age and weight-based approach is required. Paterson used a MTP protocol for a 5 year old child with massive bleeding during neurosurgery (estimated loss of between five and six blood volumes over 1.5 hr, Figure 4). [xlii] The first blood volume was replaced with crystalloid (40 ml/kg), RBCs (30 ml/kg) and plasma (20 mL/kg FFP). RBCs, plasma, platelets, cryoprecipitate and rFVIIA were used subsequently. The child survived. Further studies are necessary to validate use of MTP in children.

SUMMARY

Massive hemorrhage and resuscitation can result in refractory coagulopathy if not aggressively treated. The use of MTPs facilitate rapid availability of components in an increased ratio of plasma and platelets to RBCs. Increased ratios of plasma and platelets to RBCs and their timely administration are thought to improved outcome in trauma, decrease coagulopathy and transfusion requirements based on retrospective data. Large volumes of plasma are required to correct coagulopathy, so early administration is presumably more efficacious. The approach would be different when specific factor concentrates are used.[xliii] Point of care viscoelastic assays may allow for goal directed therapy in coagulopathy of trauma and massive transfusion including the use of antifibrinolytics when appropriate (although localized fibrinolysis may not be seen on TEG/ROTEM). Single agent therapy such as rFVIIa may have a role in coagulopathic trauma patients but safety is still a concern. A restrictive transfusion strategy should be adopted once hemorrhage is controlled to minimize unnecessary exposure to blood.

MTP practice is still fraught with many unresolved issues such as use of fibrinogen and/or prothrombin complex concentrate and blunt vs penetrating trauma. Understanding the mechanism of hemorrhage is not universal and is different in the obstetrical population as it is in pediatric or cardiovascular patients. This may add to the limitation of universal adoption of a single ratio driven MTP. Well designed, prospective randomized trials are required to determine optimal transfusion ratios and timing of blood component administration.

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