Damage Control Resuscitation:
The Case For Early Use of Blood Products and Hypertonic Saline in Exsanguinating Trauma Victims

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Abstract

Resuscitation of massively traumatized patients is physiologically complex, time-dependent, and a significant resource management matter often associated with poor survival rates. Retrospective medical evidence accumulated from combat trauma admissions to the Joint Theater Trauma Registry (JTTR) 2003-2007 supports swift replacement blood products when total blood volume losses of 30-40% or greater has occurred. Replacement plasma, packed red blood cells, and platelets in a ratio of 1:1:1 significantly reduces trauma-related coagulopathy. Clinical management specifically avoiding acidosis and hypothermia, in conjunction with administration of specific blood products, or fresh whole blood, will blunt the emergence of the 'lethal triad.' Limited Level 1Trauma Center prospective evidence based on massive blood transfusion of penetrating torso injuries supports the JTTR data.

Large resuscitative volumes of isotonic crystalloids are detrimental to survival outcomes of trauma patients. Crystalloid associated dilutional coagulopathy and the initiation of multiple cytotoxic cascades results in terminal cyto-pathology, abdominal compartment syndrome, multi-organ failure, sepsis, and death. Limited crystalloid infusion should accompany medical and surgical management of these complex trauma patients, establishing permissive hypotension until damage control surgical interventions are provided.

Compelling evidence exists for use of hypertonic saline in resuscitation of acute anemic hypovolemia. FDA has not approved its use in trauma resuscitation.

Background

Traumatic injuries have a devastating human global impact. In 2000, approximately five million deaths were attributed to crush and penetrating injuries. Major trauma has a death rate of 83 per 100,000 population and accounts for 9% of global deaths. Victims of penetrating traumatic events who arrive alive at trauma centers and who subsequently die do so because of multi-organ failure and sepsis, not due to blood loss exigent to wounds sustained from those traumatic events. These events typically occur in males between the ages of 1-44 years. Trauma is the leading cause of pediatric deaths. Traumatic events within the continental United States account for 37 million emergency department visits annually and 2.6 million hospital admissions and account for one death every three minutes within the US.

The monetary impact to the economy in 2000 was $406 billion, of which $80 billion was due to direct medical costs, and $326 billion was calculated as indirect costs to the economy due to lost productivity. Between 01 January and 15 August 2011, the total number of deaths occurring from traumatic injuries has eclipsed 134,792.[1] In comparison, during the interval 2002-2010, the total number of combat deaths recorded for the wars in Afghanistan and Iraq, Operation Enduring Freedom, and Operation Iraqi Freedom respectively, has reached 5,000. The total number of survivable injuries during this same period has reached 34,000, excluding injuries associated with traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD).

The process of resuscitating trauma victims who sustain massive blood loss is a multifaceted, time-dependent clini-

cal challenge. Despite rapid deployment of first responders, rapid transport of trauma victims to established Trauma Units, prompt use of modern interventions, and monitoring techniques in well equipped intensive care units, mortality rates continue to remain high.

Advanced Trauma Life Support (ATLS)[2] guidelines developed by the American College of Surgeons (ACOS) have emphasized specific practice management interventions for all trauma victims. A pivotal concept that has remained central, and an immutable belief within the ATLS recommendations, has been that optimal hemodynamic function would be restored by rapidly infusing isotonic crystalloid solution in a ratio of 3:1 saline to blood loss, or at a greater ratio up to 1:8 for massive blood loss.[3,4] Repletion of deficient intravascular volume and its associated contracted interstitial fluid was considered an essential step to restore physiological function in acutely anemic trauma victims.

High volume acute blood loss or persistent on-going blood losses require banked blood products to be transfused using type specific packed red blood cells or universal donor cells (type O) when these would be made available from the blood bank. Women of child-bearing age should be administered Rh negative red cells to avoid complications of antibody formation against Rh positive donor cells. These antibodies, which are responsible for carnicterus and fetal hydrops, will seriously degrade fetal viability in future pregnancies.

In the past, surgical specialties have tacitly stated that trauma victims die from increased clotting complications and not because of extensive blood loss, a belief that has been anchored in the reliance upon ligation and not upon scientific evidence. However, current concepts in cell biology provide clarity to defined cascades of dynamic molecular biochemistry and biophysics, permitting an understanding of the properties of intracellular and extracellular inflammatory cascades mediated by epitopic cell signaling. These entities have significantly altered prevailing scientific appreciation of trauma related tissue and organ effects that devolve from near exsanguinations and shock states.[5,6,7]

The 'Lethal Triad'

Within the context of severe hemorrhage, anticipated coagulopathy must be expeditiously managed to avoid later manifesting coagulopathic states. The expression of these is seen to be amplified when associated with hypothermia and acidosis. Hypocoagulation, hypothermia, and metabolic acidosis are collectively termed the 'lethal triad.'[8] The mortality rate increases significantly with one or more of these clinical markers. When malignant arrhythmias are included within the triad of extensive blood loss, hypothermia, and metabolic acidosis, the clinical severity becomes profoundly more complex with a decompensating physiologic reserve.

Anaerobic metabolism contributes directly to dysrhythmias by down regulation and functional incompetency of cell membrane ionophores. This causes significant disruption to electrical neutrality of cell walls and subsequently to the tonicity within cells via transmembrane energy losses. Thus, declining cardio-myofibril competency and critically diminishing cardiac index and reserve leads to end stage malignant rhythms and cardiac standstill.

Consequently, attention must be directed toward terminating unabated blood loss and avoiding early coagulopathic states by establishing environmental conditions conducive to maintaining core body temperatures of greater than 35°C. Acidemia due to tissue hypoperfusion corrected by restoring vascular volume will result in increased perfusion pressure, which will then dislodge immature fibrin clots located at sites of intimal vascular injury.

This is better managed by permissive hypotension and prompt damage control surgery, thereby avoiding the consequences associated with persistent blood loss, a condition termed 'the bloody vicious cycle.'[9]

Basic Science Evidence

Comprehension of basic science cell physiology, epitopic cell signaling, and gene function provides credible evidence for permitting recognition of the cytotoxic effects of crystalloids (L-form and racemic lactated Ringer's solution, normal saline) and colloids, all of which directly impinge upon the coagulation cascade.[6] Isotonic crystalloids initiate activity associated with the neutrophil oxidative burst, dilute essential cofactors within the plasma, and are responsible for delayed and deficient clotting, the consequence of which is continued bleeding from injured sites. Additionally, infusing solutions having low pH values, such as normal saline and lactated Ringers, will further augment in vivo hypo-coagulation. This effect is distinct and separate from disseminated intravascular coagulopathy (DIC).

Intravascular volume repletion with crystalloids, while improving systemic blood pressure, will cause immature platelet clots to disengage from the point of intimal tear, resulting in continued hemorrhage. Un-warmed crystalloids inherently adversely impact thermogenesis. Additionally, cellular energy, which is normally derived from mitochondrial aerobic metabolism, is lost by the effects of crystalloid cytotoxicity. The mechanism is seen to be from direct inhibition of cell membrane ionophore function. This energy loss, known as metabolic entropy, further degrades the homeostasis of thermogenesis. Isotonic crystalloids prime immunogenic modulation of neutrophilic burst activity and degrade intrinsic metabolic capability to initiate humeral and cell mediated function. Thus, sepsis, acute respiratory distress syndrome (ARDS), and multiple organ failure (MOF) will rapidly evolve.

In contradistinction to isotonic saline, hypertonic saline solution suppresses neutrophilic burst activity, minimizes third spacing of intravascular infusates, and offsets apoptosis of various organ cell lines, making this a temporary but effective fluid for resuscitation of trauma victims. NATO countries have authorized 3% and 7.5% saline for military surgical use.[5] The FDA has not approved the use of hypertonic saline solutions for

combat resuscitation nor for civilian surgical conditions related to massive blood loss. Three percent saline is widely used in US intensive care units for medical conditions requiring vascular support and repletion of serum sodium.

The Basis of JTTR Clinical Practice Guidelines[20]

Clinical evidence for a paradigm shift in the early management of massive blood loss in trauma victims has been provided by robust retrospective documentation compiled by the JTTR.[17]

Published JTTR surgical records from 2003-2007, of which 708 trauma records underwent multivariate logistic regression analysis, concluded that at 48 hours, increased survival rates (82% vs. 62% $p<0.001$) occurred in those casualties receiving fresh whole blood or aphoretic platelets when compared to casualties not receiving either whole blood or platelets. Survival rates at 30 days were sustained (62% vs.50% $p= 0.04$).[18] This analysis suggests the use of whole blood and aphoretic platelets are independent predictors of survival. When administered in a 1:1:1 ratio of PRBCs:plasma:platelets, this resulted in a reduction of long term mortality from 65% to 19%.[23]

Retrospective data from 466 massively transfused civilian patients appear concordant with the conclusions that emerged from the JTTR analysis. These observations present compelling reasons to reconsider the logic of continuing to follow the principles of ATLS in those situations where penetrating chest injuries are present. Based on JTTR and other limited prospective civilian trauma data[19] it would be prudent to carefully monitor how much and how rapidly, or indeed should large volumes of crystalloids be administered as the initial strategy for the resuscitation of complex trauma victims who have lost 30-40% of their blood volume. It seems that keeping the resuscitative crystalloid volume to less then 250 mls is the approach to be undertaken. This would then be closely followed by rapidly infusing red blood cells, plasma, and platelets in high ratio.[10,11,12,13,14,15] To date this strategy has not achieved a consensus amongst civilian traumatologists, unlike military surgeons who employ the JTTR clinical practice guidelines (CPG).

Joint Theater Trauma Registry Clinical Practice Guidelines[20]

Laboratory and clinical parameters are used in management planning for exsanguinating trauma patients. These are: 1) INR greater than 1.5; 2) base deficit greater than 6.0; 3) hemoglobin less than 12; 4) temperature less than 96F; 5) systolic blood pressure less than 90mm Hg. The mortality rate associated with massive blood loss trauma is seen to be 25% with one or more of these markers being present.

JTTR CPG requires the administration of six units of cross matched packed red blood cells (PRBCs), six units of plasma, and six pack platelets (equivalent to 1 pack aphoretic platelets) in a ratio of 1:1:1. In addition, recombinant activated factor VII (rFVIIa)[21] is administered as 100mcg/kg intravenously, repeated every 20 minutes for up to four doses when it becomes clinically evident that at least ten units of blood will be required for resuscitation. Fresh whole blood[22] may be utilized when the Red Cross supply is depleted.

Discussion

Coagulopathic states evolve early following major trauma. This fact has been neglected and generally accepted as a consequence of resuscitation, hemodilution, and hypothermia. Civilian hospitals have limited experience with massive transfusions when compared to that experience obtained by military surgeons managing patients who have sustained extensive penetrating fragmentation wounds. These wounds are frequently accompanied by class III and IV blood losses. Additionally, appreciating the complex role played by pro-inflammatory cascades occurring within the vascular system and within the intracellular chemistry of critical organ systems of exsanguinating trauma patients, ATLS algorithms may actually be deleterious when vascular resuscitation is attempted using large volumes of crystalloids.

Data presented suggest that practice management of trauma resuscitation will likely undergo a fundamental change from previously held clinical concepts and algorithms of ATLS in order to decrease morbidity and mortality rates that currently accompany existing practice standards in the management of exsanguinating trauma.

New algorithms must be proposed emphasizing ‘minimal use’ resuscitative crystalloid infusions for casualties sustaining massive blood loss if trauma management advances are to improve survivorship and to decrease post-traumatic morbidity. Civilian trauma and emergency medicine specialists to date have given little support to this novel strategy.

Effective application of known basic science mechanisms must become rationally integrated within clinical resuscitation strategies and protocols. Aggressive crystalloid repletion of intravascular volume, especially when losses exceed 30-40% total blood volume, fails to support prevailing scientific logic. For example, plasma clotting co-factors are diluted by crystalloid volume infusion. Isotonic crystalloid cytotoxicity augments hemorrhagic diathesis. In contra distinction, hypertonic saline has not been associated with any discernable cytotoxic effects that are readily seen when large volume isotonic crystalloids are administered. Hypertonic saline is available and approved outside the US as 3% and 7.5% concentrations for trauma resuscitation. FDA approval for hypertonic saline use in trauma is under consideration.

Extensive retrospective studies generated from Combat Support Hospitals during Operation Iraqi Freedom and Operation Enduring Freedom provide encouraging data when damage

control surgery is integrated with class 4 (over 40% total blood volume) blood loss trauma victims and with the following specific actions and agents: 1) permissive hypotension is utilized; 2) fresh whole blood or packed red blood cells are promptly infused; 3) plasma volume is rapidly replaced; 4) platelets administered to replete those lost; 5) recombinant Factor VII activated (rFVIIa) administered when ten units or more of blood are required; and 6) minimal crystalloid infusion not to exceed 250 mls. Integration of these actions has contributed to measurably better survival rates (65% vs. 19%).

Retrospective Joint Theater Trauma Registry studies reveal improved survivability, less complications, earlier ventilator extubation, decreased incidence of abdominal compartment syndrome, clinically relevant reduction in post-resuscitation edema, and evidence for decreased 3rd spacing, including a quantifiable reduction in the use of blood products when high ratio PRBCs:plasma:platelets are utilized in 1:1:1 ratio. This cannot be stated for the clinical results of similar trauma injury severity situations where receiving transfusions at customary 1:3 ratio of plasma: RBC as is standard practice in the majority of US civilian hospitals.

An opinion consensus among civilian traumatologists has not been achieved regarding optimal plasma, platelet, and red blood cell ratios in massive transfusion damage control resuscitation. Recent civilian small prospective trials using a high ratio transfusion regimen, the same as those established by JTTR CPG, are consistent with outcomes reported by JTTR. Recognizing and appreciating the existence of the early presence of coagulopathy in exsanguinating casualties will result in rational transfusion strategies and resuscitation management that employ early use of blood products and very sparing use of isotonic crystalloids.

Avoidance of the 'lethal triad' (coagulopathy, hypothermia, and acidosis) will substantially improve the rate of successful resuscitative outcomes.

Damage Control Anesthesia[23]

During damage control resuscitation, anesthesia management is uniquely different from procedural sedation and rapid sequence intubation as performed on hemo-dynamically stable patients in whom intravascular volume is not a critical factor. In hypovolemic anemic shock anesthesia management requires close management to avoid precipitous fluctuations of systemic blood pressure. Variations in blood pressure will occur early during induction, sedation, and when neuromuscular blockade agents are administered for acquisition of mechanical airway control. Pain control and achieving dissociative anesthesia especially sensitize the vascular system to wide oscillations of systemic blood pressure.

The loss of vasoconstrictive reflexes characteristic of shock states, or when using induction agents in conjunction with massive hypovolemia, will significantly impact the potential for the clinical expression of the magnitude of residual catecholamine load and the subsequent catechole surge is expectantly severely attenuated, resulting in profound hypotension. Hypertensive episodes seen under these unstable physiological conditions are believed to disrupt polymerizing collagen found within immature fibrin clots that are localizing at sites of vascular injury.

To manage these critical blood pressure oscillations, blood products consisting of PRBCs, plasma, and platelets must be administered rapidly while incrementally titrating small doses of Fentanyl in amounts not exceeding about one-fifth of that commonly used during RSI. The goal is to establish a mean arterial pressure of 65mmHg, which is approximately equal to a systolic pressure of 70mmHg. Limited infusion of 250 mls of crystalloid is permitted during this phase of the damage control resuscitation.

Summary

Understanding relevant biochemical cascades associated with cell function and their epitopic triggers operating diverse gene functions that impact interleukin, bradykinin, neutrophil burst oxidation, intravascular coagulation functions, and their relationship with infusible crystalloid toxicity together with their apparent close relationship with trauma related coagulopathy, provides a viable scientific basis for recommending a substantial practice change in how complex trauma resuscitation should be managed.

An extensive retrospective series of critically wounded combat personnel during Operation Iraqi Freedom and Operation Enduring Freedom admitted to the JTTR 2003-2007, in whom massive blood loss had occurred, show strong clinical concordance with currently available basic science cell physiology and the justifiable use of plasma, platelets, and RBCs in the ratio of 1:1:1. Recent limited civilian prospective studies have provided similar improved survival outcomes in trauma victims sustaining massive blood loss.

Avoidance of coagulopathy, prevention or reversal of hypothermia, and acidosis (lethal triad) in casualties who have sustained massive blood loss who require salvage resuscitation, are best managed by applying new key concepts that reflect improved comprehension of the intrinsic pathophysiology of trauma resuscitation. Applying interventions that are concordant within both basic science and emerging clinical evidence unique to trauma resuscitation will reduce morbidity and mortality within a subgroup of exsanguinating trauma victims.

These changes must be appreciated and managed in a longitudinally consistent manner by paramedics, Emergency Medicine, critical-care transport, and Trauma Teams, if improved survivability is to materialize.

Permissive hypotension, prompt use of blood products, and hypertonic crystalloid solutions, the latter when approved by the FDA, appear likely to optimize the survivability of the mas-

sively injured patient. Avoiding large volumes of isotonic crystalloids, preventing hypothermia and acidosis have been shown to decrease morbidity and mortality. ATLS algorithms should now reflect these recent encouraging trends in trauma stabilization and its subsequent definitive management.

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