

Trauma Update 2010

Mark H. Chandler, MD
 Lieutenant Colonel
 COARNG State Surgeon

Trauma Update 2010 Outline

- GWOT's lessons learned on Trauma
- Damage Control Resuscitation
- Trauma Induced Coagulopathy
- Massive Transfusion Protocols
- Predictive Models for Massive Transfusion
- Recombinant Activated Factor VII
- Ratio Wars
- Whole Blood

Global War on Terrorism (GWOT)

- OIF: Operation Iraqi Freedom, conventional war officially began March 20, 2003.
 - 4362 US Killed
 - 31,616 US Wounded
- OEF: Operation Enduring Freedom, combat operations began October 7, 2001.
 - 975 US Killed
 - 4748 US Wounded
- 5337 US killed, 36,364 US wounded GWOT

Lethality of War Wounds of U.S. Soldiers

CONFLICT	WIA/KIA	KIA	LETHALITY
Revolutionary War, 1775-1783	10, 623	4,435	42%
War of 1812, 1812-1815	6,765	2,260	33%
Mexican War, 1846-1848	5,885	1,733	29%
Civil War (Union Forces), 1861-1865	422,295	140,414	33%
Spanish-American War, 1898	2,047	385	19%
World War I, 1917-1918	257,404	53,402	21%
World War II, 1941-1945	963,403	291,557	30%
Korean War, 1950-1953	137,025	33,741	25%
Vietnam War, 1961-1973	200,727	47,424	24%
Persian Gulf War, 1990-1991	614	147	24%
War in Iraq/Afghanistan, 2001-present	36,364	5,337	15%





United States Army Institute of Surgical Research



» Located at Fort Sam Houston, San Antonio, TX

» Mission to provide combat casualty care medical solutions/products for injured soldiers from self-aid through definitive care across the full spectrum of military operations.



» Conducts research and generates considerable literature from trauma lessons learned in OIF/OEF.

» Maintains the Joint Theater Trauma Registry (JTTR): the data repository of all DoD trauma related data.

Damage Control Resuscitation

CLINICAL REVIEW

For the full versions of these articles see bmj.com

Damage control resuscitation for patients with major trauma

Jan O Jansen,^a Rhys Thomas,^a Malcolm A Loudon,^a Adam Brooks^a

Damage control resuscitation: A sensible approach to the exsanguinating surgical patient

MAJ (P) Alec C. Beeckley, MD, FACS

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Blood Reviews



journal homepage: www.elsevier.com/locate/br

REVIEW

Resuscitation and transfusion principles for traumatic hemorrhagic shock

Philip C. Spinella^{a,*}, John B. Holcomb^{b,†}

^aAssociate Professor of Pediatrics, University of Connecticut, Pediatric Intensive Care, Department of Pediatrics, Medical Director Surgical Critical Care, Department of Surgery, Connecticut Children's Medical Center, 202 Washington St, Hartford, CT 06106, United States

^bProfessor of Surgery, Chief, Division of Acute Care Surgery, Director, Center for Translational Injury Research, University of Texas Health Science Center, 6438 Fawcett St, Suite 1300 Houston, TX 77030, United States

What is Damage Control Resuscitation (DCR)?

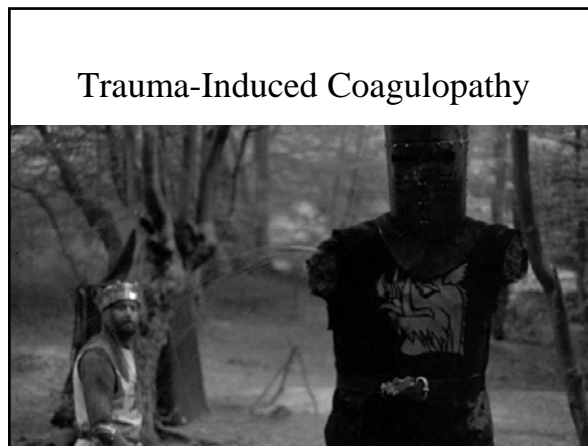
- Early/aggressive strategy to prevent and treat hemorrhagic shock for patients with severe life threatening traumatic injuries, usually in the setting of massive transfusion (>10 units PRBC/24 hrs)
- So named for its coupling with “Damage Control Surgery.”
- “Staying out of trouble instead of getting into trouble.”
- Has undergone recent refinement in military circles mainly because of the lessons learned from OIF/OEF

Traditional Trauma Resuscitation

- Immediate administration of crystalloid fluid (this is still taught in most ATLS courses)
- After an initial resuscitation with crystalloid, PRBCs are started for continued evidence of shock
- Addition of plasma and platelets are only after a certain threshold of PRBCs (e.g. 8-10u) has been reached
- Treatment of hypothermia, acidosis and coagulopathy is part of secondary resuscitation that usually does not begin in earnest until the patient reaches the ICU

The key aspects of DCR

- Rapid recognition of “trauma-induced coagulopathy” (massive transfusion prediction)
- Permissive hypotension/minimizing use of crystalloids
- Rapid/definitive control of bleeding
- Early prevention of hypothermia, acidosis
- Early transfusion of RBC (fresh):plasma:PLTs in a 1:1:1 unit ratio
- Use of thawed plasma and Fresh Whole Blood (when available)
- Appropriate use of rFVIIa and fibrinogen containing products such as cryoprecipitate
- When available, POC coagulation assays such as rapid thromboelastography (rTEG) to guide administration of blood products and hemostatic adjuncts



Trauma-induced coagulopathy

- Traditional view of coagulopathy in trauma
 - Dilution from fluid resuscitation
 - Procoagulant protease losses from consumption/bleeding
 - Dysfunction related to acidosis and hypothermia
- Recent literature suggests that coagulopathy that attends trauma is an independent multifactorial entity

The Journal of TRAUMA® Injury, Infection, and Critical Care

Review Article

The Coagulopathy of Trauma: A Review of Mechanisms

John R. Hess, MD, MPH, FACP, FAAAS, Karim Brohi, MD, Richard P. Dutton, MD, MBA, Carl J. Hauser, MD, FACS, FCCM, John B. Holcomb, MD, FACS, Yurana Kluger, MD, Kevin Mackway-Jones, MD, FRCP, FRCS, FCEM, Michael J. Parr, MB, BS, FRCP, FRCA, FANZCA, FJFICM, Sandro B. Ricoli, MD, PhD, FRCSC, Tetsuo Yukioka, MD, David B. Hoyt, MD, FACS, and Bertil Bouillon, MD

Background: Bleeding is the most frequent cause of preventable death after severe injury. Coagulopathy associated with severe injury complicates the control of bleeding and is associated with increased mortality and mortality in trauma patients. The causes and mechanisms are multiple and yet to be clearly defined.

Methods: Articles addressing the causes and consequences of trauma-associated coagulopathy were identified and reviewed. Clinical situations in which the various mechanistic causes are important were sought along with quantitative estimates of their importance.

Results: Coagulopathy associated with traumatic injury is the result of multiple independent but interacting mechanisms. Early coagulopathy is driven by shock and requires thrombin generation from tissue injury as an initiator. Initiation of coagulation occurs with activation of anticoagulant and fibrinolytic pathways. This Acute Coagulopathy of Trauma-Shock is altered by subsequent events and medical therapies, in particular acidemia, hypothermia, and dilution. There is significant interplay between all mechanisms.

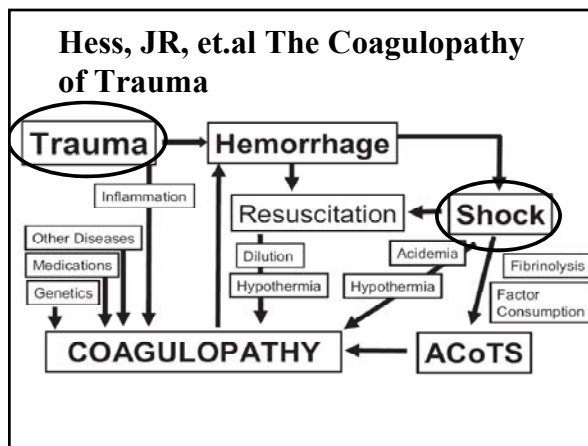
Conclusions: There is limited understanding of the mechanisms by which tissue trauma, shock, and inflammation initiate trauma coagulopathy. Acute Coagulopathy of Trauma-Shock should be considered distinct from disseminated intravascular coagulation as described in other conditions. Rapid diagnosis and directed interventions are important areas for future research.

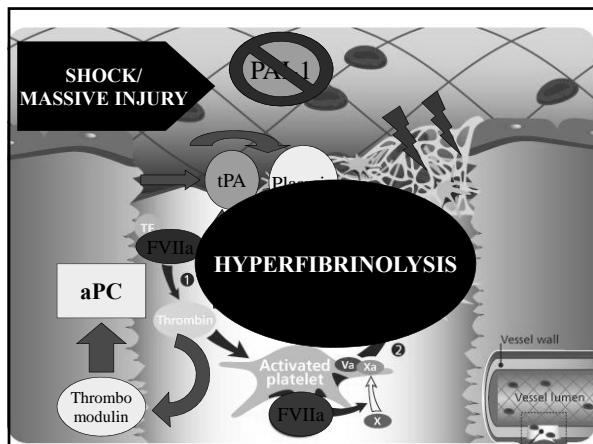
Key Words: Coagulopathy, Trauma, Shock, Mechanism, Review.

J Trauma. 2008;65:748-754.

Hess, JR, et.al. Coagulopathy of Trauma

- Six key initiators of the coagulopathy of trauma:
 - Tissue trauma
 - Shock
 - Hemodilution
 - Hypothermia
 - Acidemia
 - Inflammation
- Which predominates depends upon:
 - Nature and severity of tissue injuries
 - Degree of circulatory physiologic derangement
 - Deleterious side effects of subsequent medical therapies





Hess, JR, et.al, Coagulopathy of Trauma

- Hyperfibrinolysis meant to limit clot propagation
- High energy injury leads to many sites of endothelial disruption; localization is lost
- Not “DIC:” similarities, but different underlying mechanisms, earlier onset, and relative sparing of platelets and fibrinogen.
- Various names: Acute Traumatic Coagulopathy, Early Coagulopathy of Trauma, Trauma-Induced Coagulopathy
- “ACoTS” Acute Coagulopathy of Trauma-Shock

Massive Transfusion Protocols

The Journal of TRAUMA® Injury, Infection, and Critical Care

Damage Control Hematology: The Impact of a Trauma Exsanguination Protocol on Survival and Blood Product Utilization

Byron A. Cotton, MD, Oliver L. Gunter, MD, James Ibell, MD, Brigham K. Au, BS, Amy M. Robertson, MD, John A. Morris, Jr., MD, Paul St. Jacques, MD, and Pampee P. Young, MD, PhD

Background: The importance of early and aggressive management of trauma-related coagulopathy remains poorly understood. We hypothesized that a trauma exsanguination protocol (TEP) that systematically provides specified numbers and types of blood components immediately upon initiation of resuscitation would improve survival and reduce overall blood product consumption among the most severely injured patients.

Methods: We recently implemented a TEP, which involves the immediate and continued release of blood products from the blood bank in a predefined ratio of 10 units of packed red blood cells (PRBC) to 4 units of fresh frozen plasma to 2 units of platelets. All TEP activations from February 1, 2006 to July 31, 2007 were retrospectively evaluated. A comparison cohort (pre-TEP) was selected from all trauma admissions between August 1, 2004 and January 31, 2006 that (1) underwent immediate surgery by the trauma team and (2) received greater than 10 units of PRBC in the first 24 hours. Multivariable analysis was performed to compare mortality and overall blood product consumption between the two groups.

Results: Two hundred eleven patients met inclusion criteria (117 pre-TEP, 94 TEPs). Age, sex, and Injury Severity Score were similar between the groups, whereas physiologic severity (by weighted Revised Trauma Score) and predicted survival (by trauma-related Injury Severity Score, TRISS) were worse in the TEP group (p values of 0.037 and 0.028, respectively). After controlling for age, sex, mechanism of injury, TRISS and 24-hour blood product usage, there was a 74% reduction in the odds of mortality among patients in the TEP group ($p = 0.001$). Overall blood product consumption adjusted for age, sex, mechanism of injury and TRISS was also significantly reduced in the TEP group ($p = 0.015$).

Conclusions: We have demonstrated that an exsanguination protocol, delivered in an aggressive and predefined manner, significantly reduces the odds of mortality as well as overall blood product consumption.

Key Words: Hemorrhage, Exsanguination, Trauma, Massive transfusion.

J Trauma. 2008;64:1177-1183

Cotton BA, et. al. Damage Control Hematology

- Retrospective cohort study measuring the effectiveness of a TEP (Trauma Exsanguination Protocol) in terms of survival and overall blood product consumption among most severely injured trauma patients
- Two cohorts:
 - 94 TEP patients from activation of TEP 1 FEB 06 – 31 JUL 07
 - 211 Pre-TEP patients from 1 AUG 04 – 31 JAN 06 who underwent immediate surgery by trauma team and received > 10 u PRBC/24 hrs.
- Multivariable analysis used to compare mortality and overall blood product consumption

VUMC Trauma Exsanguination Protocol (TEP)

- Trauma Attending activates protocol (pure clinical call)
- Initial Response Products sent:
 - 10 units nonirradiated, uncrossed PRBCs
 - 4 units AB-negative FFP
 - 2 units single donor platelets
- Trauma team/blood bank determine if follow on cycle of products are needed: 6 PRBCs, 4 units FFP, 2 SD PLT
- Cryoprecipitate is available for all cycles on physician request.

Cotton, et. al.: Methods

Table 1 Baseline Characteristics and Descriptive Data of the Study Groups

Characteristic	Pre-TEP (n = 117)	TEP (n = 94)	P
Age, yr (±SD)	39.3 ± 17.7	35.5 ± 15.3	0.176
Male (%)	76	73	0.657
w-RTS (±SD)	4.45 ± 2.6	3.74 ± 2.8	0.037*
ISS (±SD)	29.8 ± 16.2	32 ± 16.8	0.217
TRISS (±SD)	0.53 ± 0.38	0.40 ± 0.39	0.029
Penetrating mechanism (%)	30	56	0.012*

* Statistically significant at $p < 0.05$.

TEP, trauma exsanguination protocol; w-RTS, weighted Revised Trauma Score; ISS, Injury Severity Score; TRISS, trauma-related Injury Severity Score.

Cotton, et. al.: Results

Table 2 Univariate Analyses of Primary and Secondary Outcome Measures

Variable	Pre-TEP (n = 117)	TEP (n = 94)	P
30-d mortality (%)	65.8	51.1	0.030*
24-h blood product use (units)	39 ± 28	31.8 ± 19	0.017*
24-h RBC use (units)	19.8 ± 12.8	18.8 ± 11.2	0.695
24-h FFP use (units)	12.4 ± 12.5	9.9 ± 7	0.595
24-h PLT use (units)	6.8 ± 7.2	3.1 ± 3.7	<0.001*
Intraoperative RBC use (units)	11.1 ± 8.5	16 ± 11.4	0.001*
Intraoperative FFP use (units)	4.3 ± 4	8.2 ± 6.8	<0.001*
Intraoperative PLT use (units)	1.1 ± 2.6	2.2 ± 2.3	<0.001*
Intraoperative crystalloid (L)	6.7 ± 4.2	4.9 ± 3.0	0.002*
Unexpected survivors (%)	5.1	22.3	<0.001*
Unexpected deaths (%)	22.2	8.5	0.007*

* Statistically significant at $p < 0.05$.

TEP, trauma exsanguination protocol; RBC, red blood cell; FFP, fresh frozen plasma; PLT, platelets.

Cotton, et. al.: Conclusion

- 74% reduction in the odds of mortality using TEP
- Although TEP patients received more intraoperative blood products, they had reduced postoperative and 24 hour product use.
- Less intraoperative crystalloid use
- Replacing “what is bled” echoes the approach advocated by the military data from OIF/OEF using DCR.
- Criticism: initiation was pure clinical call.

The Journal of TRAUMA® Injury, Infection, and Critical Care

Early Prediction of Massive Transfusion in Trauma: Simple as ABC (Assessment of Blood Consumption)?

Timothy C. Nunez, MD, Igor V. Voskresensky, MD, Lesly A. Dossert, MD, MPH, Ricky Shinall, BS, William D. Dutton, MD, and Bryan A. Cotton, MD

Background: Massive transfusion (MT) occurs in about 3% of civilian and 8% of military trauma patients. Although many centers have implemented MT protocols, most do not have a standardized initiation policy. The purpose of this study was to validate previously described MT scoring systems and compare these to a simplified nonlaboratory dependent scoring system (Assessment of Blood Consumption [ABC] score).

Methods: Retrospective cohort of all level I adult trauma patients transported directly from the scene (July 2005 to June 2006). Trauma-Associated Severe Hemorrhage (TASH) and McLaughlin scores

calculated according to published methods. ABC score was assigned based on four nonweighted parameters: penetrating mechanism, positive focused assessment sonography for trauma, arrival systolic blood pressure of 90 mm Hg or less, and arrival heart rate ≥ 120 bpm. Area under the receiver operating characteristic curve (AUROC) used to compare scoring systems.

Results: Five hundred ninety-six patients were available for analysis; and the overall MT rate of 12.4%. Patients receiving MT had higher TASH (median, 6 vs. 13; $p < 0.001$), McLaughlin (median, 24 vs. 34; $p < 0.001$) and ABC (median, 1 vs. 2; $p < 0.001$) scores. TASH (AUROC =

0.842), McLaughlin (AUROC = 0.846), and ABC (AUROC = 0.842) scores were all good predictors of MT, and the difference between the scores was not statistically significant. ABC score of 2 or greater was 75% sensitive and 86% specific for predicting MT (correctly classified 85%).

Conclusions: The ABC score, which uses nonlaboratory, nonweighted parameters, is a simple and accurate in identifying patients who will require MT as compared with those previously published scores.

Key Words: Hemorrhage, Trauma, Massive transfusion, Prediction, Scoring systems.

J Trauma. 2009;66:346–352.

Nunez TC, et. al., Early Prediction of Massive Transfusion in Trauma

- Purpose: “Validate previously described Massive Transfusion (MT) scoring systems and compare these to a simplified nonlaboratory dependent system
- Assessment of Blood Consumption (ABC) Score
- Retrospective cohort of all level I trauma activation patients transported directly from scene July 05-June 06
- AUROC (Area under the Receiver Operating Characteristic Curve) used to compare scoring systems

TASH: Trauma-Associated Severe Hemorrhage

- Yucel N, et. al. Trauma Associated Severe Hemorrhage (TASH)-Score: probability of mass transfusion as surrogate for life threatening hemorrhage after multiple trauma. *J Trauma*. 2006;60:1228–1236.
- Uses 7 independent weighted variables: blood pressure, gender, hemoglobin, FAST, pulse, base excess, presence of extremity/pelvic fractures
- 16 total scores that need to be memorized, and scores can range from 0 – 28 (authors propose a worksheet to help calculate scores)
- Probability for MT calculated as follows:

$$p = 1/[1 + \exp(4.9 - 0.3 \times \text{TASH})]$$

McLaughlin Score

- McLaughlin DF, Niles SE, Salinas J, et al. A predictive model for massive transfusion in combat casualty patients. *J Trauma*. 2008;64:S57–S63.
- Developed using OIF casualties from the JTTR
- Four dichotomous components: HR > 105 bpm, Systolic BP < 110 mmHg, pH < 7.25, hematocrit < 32%; variables assigned values of 0 or 1 based on whether or not the value is predictive
- Final predictive equation:

$$\log(p/[1-p]) = 1.576 (0.825 \text{ SBP}) + (0.826 \text{ HR}) + (1.044 \text{ Hct}) + (0.462 \text{ pH})$$

ABC Scoring system

- VUMC Performance Improvement (PI) committee for compliance identified need for activation criteria for TEP
 - 2 general groups of “activators”: early vs. late; early activators queried independently for their activation criteria
 - ABC score: 4 dichotomous components available at the bedside:
 - Penetrating mechanism (0 no, 1 yes)
 - ED SBP of 90 mm Hg or less (0 no, 1 yes)
 - ED HR of 120 bpm or greater (0 no, 1 yes)
 - Positive FAST (0 no, 1 yes)
- The presence of any one component contributes one point to possible score, for a range of 1 to 4.

Nunez, et. al.: Results

- 596 patients included in cohort: Level I trauma activations from 1 JUL 05 – 30 JUN 06; transferred directly from the scene; received any blood during their hospitalization.
- Massive Transfusion Definition: ≥ 10 u PRBCs/24 hours
- Overall MT rate 12.7% (n = 76)
- Overall mortality rate 18.1% (n=108)

Nunez, et. al.: Discussion

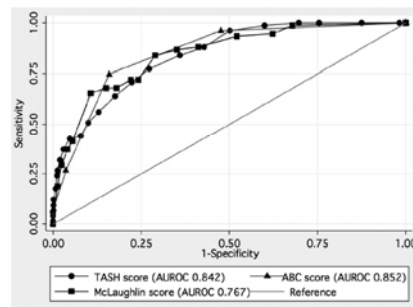
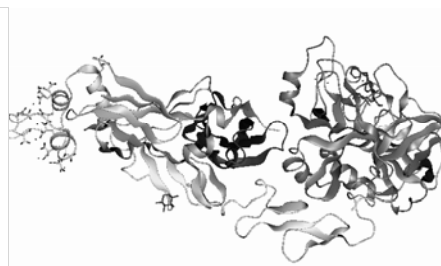


Fig. 3. AUROC for the three scoring systems.

Nunez, et. al.: Conclusion

- ABC Score: “simple, easy to remember.”
- Using cutoff 2 or greater, ABC score was 75% sensitive, 86% specific
- To be used to augment clinical judgement, not substitute it
- Limitations:
 - Retrospective application of a scoring system
 - High risk patient population; unclear how well this scoring system would fair in a study of all comers
 - FAST is highly operator dependent
 - There has been no prospective randomized trial to demonstrate the benefit of MTP

Recombinant Factor VIIa



Background rFVIIa

- Produced by Novo Nordisk, A/S (Bagsvaerd, Denmark), under the name NovoSeven, NovoSeven RT, and NiaStase
- Cost: very expensive: 80 mcg/kg for 70 kg patient = \$6408
- FDA approved for the treatment of bleeding episodes and to prevent bleeding in surgical interventions or invasive procedures in:
 - Hemophilia A or B patients with inhibitors to FVIII or FIX
 - Patients with acquired hemophilia
 - Patients with congenital Factor VII deficiency

rFVIIa use in trauma before OEF/OIF

- 1999: Kenet G, et. al. describe first use in trauma: Israeli Soldier with abdominal GSW.
- 2001: Martinowitz, et. al. publish report of first seven trauma patient who received rFVIIa
- 2002: O'Neal, et. al. describe first use of rVIIa in trauma in US: patient with multiple stab wounds, 3 operative explorations, 2 angiographic embolizations 105 PRBCs.

rFVIIa use in trauma before OEF/OIF (cont)

- 2003: Friedrich, et. al. publish landmark article of the first prospective, randomized, placebo-controlled trial of use of rFVIIa in radical prostate surgery patients:
 - Placebo arm vs. two treatment arms (20 and 40 mcg/kg)
 - Blood loss and operative time decreased in rFVIIa groups; no transfusions needed in the high dose rFVIIa group
 - No deleterious safety issues identified

The Journal of TRAUMA® Injury, Infection, and Critical Care

Recombinant Factor VIIa as Adjunctive Therapy for Bleeding Control in Severely Injured Trauma Patients: Two Parallel Randomized, Placebo-Controlled, Double-Blind Clinical Trials

Kenneth David Boffard, MD, Bruno Riva, MD, PhD, Brian Warren, MD, Phillip Iau Tsau Choong, MD, Sandro Rivoli, MD, Rolf Rossaint, MD, Maik Avelsen, MD, and Yoram Kluger, MD, for the NovoSeven Trauma Study Group

Background: Uncontrolled bleeding is a leading cause of death in trauma. Two randomized, placebo-controlled, double-blind trials (one in blunt trauma and one in penetrating trauma) were conducted simultaneously to evaluate the efficacy and safety of recombinant factor VIIa (rFVIIa) as adjunctive therapy for control of bleeding in patients with severe blunt or penetrating trauma.

Methods: Severely bleeding trauma patients were randomized to rFVIIa (20, 40, and 100 µg/kg) or placebo in addition to standard treatment. The first dose followed transfusion of the eighth red blood cell (RBC) unit, with additional doses 1 and 3 hours later. The primary endpoint

for bleeding control in patients alive at 48 hours was units of RBCs transfused within 48 hours of the first dose.

Results: Among 301 patients randomized, 143 blunt trauma patients and 154 penetrating trauma patients were eligible for analysis. In blunt trauma, RBC transfusion was significantly reduced with rFVIIa relative to placebo (estimated reduction of 2.6 RBC units, $p = 0.02$), and the need for massive transfusion (≥ 20 units of RBCs) was reduced (14% vs. 33% of patients; $p = 0.03$). In penetrating trauma, similar analyses showed trends toward rFVIIa reducing RBC transfusion (estimated reduction of 1.0 RBC unit, $p = 0.10$) and massive transfusion (7% vs. 19%; $p = 0.08$). Trends toward a reduction in mortality and critical complications were observed; adverse events including thromboembolic events were evenly distributed between treatment groups.

Conclusions: Recombinant FVIIa resulted in a significant reduction in RBC transfusion in severe blunt trauma. Similar trends were observed in penetrating trauma. The safety of rFVIIa was established in these trauma populations within the investigated dose range.

Key Words: Trauma, Blunt trauma, Penetrating trauma, Recombinant factor VIIa, Hemorrhage, Coagulopathy, Blood transfusion, Massive transfusion.

J Trauma. 2005;59:8-15.

Boffard, et. al.: Methods

- 143 blunt trauma patients, 134 penetrating trauma patients from March 2002 to September 2003
- Primary endpoint: number of RBC units transfused during the 48 hrs after the first dose of trial product.
- Other outcomes measured: need for other transfusion products, mortality, days on the ventilator, days in ICU.
- Critical complications: death, MOF, ARDS

Boffard, et. al. Results

- Blunt Trauma
 - 48 hour RBC requirement reduced by 2.6 units in rFVIIa group
 - Massive transfusion was reduced from 20 of 61 (33%) patients in the placebo group to 8 of 56 (14%) in the rFVIIa group.
- Penetrating Trauma
 - In patients with penetrating trauma, no significant effect of rFVIIa was observed with respect to 48-hour RBC requirements with an RBC reduction of 1.0 unit ($p = 0.10$).
 - Massive transfusion in penetrating trauma was reduced from 10 of 54 (19%) patients in the placebo group to 4 of 58 (7%) in the rFVIIa group.
- Adverse Events: rFVIIa did not increase the incidence of adverse events, including thromboembolism and systemic coagulation, and was also associated with a trend toward fewer critical complications such as MOF and ARDS.

The Journal of TRAUMA® Injury, Infection, and Critical Care

The Effect of Recombinant Activated Factor VII on Mortality in Combat-Related Casualties With Severe Trauma and Massive Transfusion

Philip C. Spinella, MD, Jeremy G. Perkins, MD, Daniel F. McLaughlin, MD, Sarah E. Niles, MD, MPH, Kurt W. Grathwohl, MD, Alec C. Beckley, MD, Jose Salinas, PhD, Sumaru Mehta, MD, Charles E. Wade, PhD, and John B. Holcomb, MD

Background: The majority of patients with potentially survivable combat-related injuries die from hemorrhage. Our objective was to determine whether the use of recombinant activated factor VII (rFVIIa) decreased mortality in combat casualties with severe trauma who received massive transfusion and if its use was associated with increased severe thrombotic events.

Methods: We retrospectively reviewed a database of combat casualty patients with severe trauma (Injury Severity Score [ISS] >15) and massive transfusion (red blood cell [RBC] ≥10 units/24 hours) admitted to one combat support hospital in Baghdad, Iraq, between December 2003 and October 2005. Admission vital signs and laboratory data, blood

products, ISS, 24-hour and 30-day mortality, and severe thrombotic events were compared between patients who received rFVIIa (rFVIIa+) and did not receive rFVIIa (rFVIIa-).

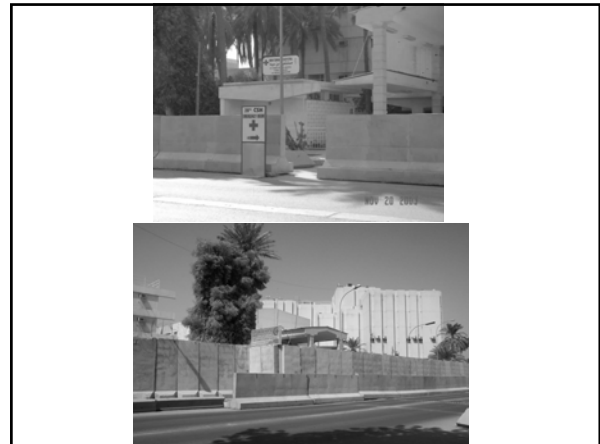
Results: Of 124 patients in this study, 49 patients received rFVIIa and 75 did not. ISS, laboratory values, and admission vitals did not differ between rFVIIa+ and rFVIIa- groups, except for systolic blood pressure (mean [SD] 105 ± 13 and 97 ± 76, $p = 0.02$ and temperature (°F) 96.3 ± 2.1 and 98.7 ± 2.2, $p = 0.03$, respectively. Interactions between all vital signs and laboratory values measured upon admission, to include systolic blood pressure and temperature, were not significant when measured between rFVIIa use and 30-day mortality. Twenty-four-hour mor-

tality was 7 of 49 (14%) in rFVIIa+ and 26 of 75 (35%) in rFVIIa-, ($p = 0.01$); 30-day mortality was 15 of 49 (31%) and 38 of 75 (51%), ($p = 0.03$). Death from hemorrhage was 8 of 14 (57%) for rFVIIa+ patients compared with 29 of 31 (78%) for rFVIIa- patients, ($p = 0.12$). The incidence of severe thrombotic events was similar in both groups.

Conclusions: The early use of rFVIIa was associated with decreased 24-hour mortality in severely injured combat casualties requiring massive transfusion, but was not associated with increased risk of severe thrombotic events.

Key Words: Recombinant FVIIa, Trauma, Mortality, Hemorrhage, Coagulopathy, War.

J Trauma. 2006;61:286-294.



Spinella, et. al.: study design

- Retrospective analysis using the Joint Theater Trauma Registry (JTTR) severe trauma at one CSH from Dec 2003 to Oct 2005
- Objective #1: To determine whether rFVIIa decreased mortality in combat-casualties from severe trauma who received massive transfusions.
- Objective #2: To determine if rFVIIa is associated with increased severe thrombotic events
- 124 patients: 49 MT rFVIIa patients, 75 MT non-rFVIIa patients (92% had penetrating trauma)

Spinella, et. al.: Results

- 12 hour mortality: 6 of 49 (12%) for the rFVIIa group and 25 of 75 (33%) for the rFVIIa group ($p = 0.008$).
- 24 hour mortality was 7 of 49 (14%) for rFVIIa and 26 of 75 (35%) for rFVIIa patients ($p = 0.01$).
- 30 day mortality was 15 of 49 (31%) for rFVIIa and 38 of 75 (51%) for rFVIIa patients ($p = 0.03$).

Spinella, et. Al.: Results (cont.)

- Of 124 patients in study, 53 died
 - rFVIIa patients median time of death of 43 hrs. (2.7-155 hrs; $p=0.035$) vs. 3.7 hrs. among non-rFVIIa patients
 - Of the patients who died, 40% (6 of 15) of rFVIIa patients died within 12 hrs vs. 63% (25 of 38) of nn-rFVIIa patients.

Spinella, et.al.: Results

Physiologic Cause of Death (n = 53)	rFVIIa (n = 35)	rFVIIa- (n = 18)	p Value
Hemorrhage n = 37	20/37 (28%)	17/18 (94%)	0.12
Pulmonary failure n = 3	1/3 (11%)	2/14 (14%)	0.18
CNS injury n = 7	4/37 (11%)	3/14 (21%)	0.37
Sepsis n = 3	2/37 (5%)	1/14 (7%)	0.6
MOF n = 2	2/37 (5%)	0/14 (0%)	1.00

Data on physiologic cause of death available for 51 of 53 deaths reported.

Variable	rFVIIa N = 75	rFVIIa- N = 49	p Value
Bacteremia	12/75 (16%)	3/49 (6%)	0.1
Thrombotic events	0/75	2/49 (4%)	1.0
ARDS	3/75 (4%)	1/49 (2%)	1.00
MOF	4/75 (5%)	1/49 (2%)	0.65

rFVIIa, recombinant activated factor VII; ARDS, acute respiratory distress syndrome; MOF, multi-organ failure.

- Of 124 patients in study, 53 died
- rFVIIa patients median time of death of 43 hrs. (2.7-155 hrs; $p=0.035$) vs. 3.7 hrs. among non-rFVIIa patients
- Incidence of severe thrombotic events (DVT, PE, and stroke), bacteremia, ARDS and MOF similar in both groups

Spinella, et. al: Discussion

- How do you account for the diminished mortality seen here, but not seen in Boffard, et. al?
 - Increased injury severity despite similar ISS
 - Increased indicators of admission hypoperfusion among patients in this study.
 - Higher overall mortality in this study compared to Boffard, et. al. (43% vs. 26%)

Ratio Wars

Author	Design	Single or multicenter	Number of MT patients	Plasma:RBC transfusion ratio	Inclusion criteria	Exclusion criteria	Total cases randomized	Main results	Mortality (%) low to high ratio group	Significant limitations
Borgman MA ¹	R	Multi ²	246	1:1	≥ 10 RBC in 24 h	Yielded from another facility	246	1 (AE)	65-34-39	Did not include early deaths subject to transfusion time
Margolis JR ³	RCTD	Multi	713	1:1	≥ 10 RBC in 24 h	Death in ED	ED and ICU 243	1 (AE)	45-36-30	No all for confounding variables with mortality
Holcomb JB ⁴	R	Multi	466	Mixed	≥ 10 RBC in 24 h	Death < 30 min admission	243	1 (AE)	47-27	No all for confounding variables with mortality
Sperry JR ⁵	RCTD	Multi	611	1:1	≥ 10 RBC in 12 h	Preventing injury	12 h	1 (AE)	30-28	Did not include early deaths subject to transfusion time
Gustafson CL ⁶	R	Single	258	Mixed	≥ 10 RBC in 24 h	Death in ED	24 h	1 (AE)	42-41	Did not include measures of acidosis and coagulopathy
DeChamone JC ⁷	R	Single	131	Mixed	≥ 10 RBC in 24 h	Death in ED	24 h	1 (AE)	88-26	Did not include measures of acidosis and coagulopathy
Trice KA ⁸	R	Multi	452	Mixed	≥ 10 RBC in 24 h	Death < 30 min admission	416	1 (AE)	51-41-25	Did not include measures of acidosis and coagulopathy
Griffith JR ⁹	R	Single	133	Mixed	≥ 10 RBC in 6 h	Severe TBI or cause of death	6 h	1 (AE)	77-37-55	Underpowered
Spahn DR ¹⁰	P	Single	81	Not reported for MT patients	≥ 10 RBC in 24 h	Death in ED or OR	24 h	1 (AE)	14 (all patients)	Underpowered
Sperry JR ¹¹	R	Single	134	Mixed	≥ 10 RBC in 24 h	None	24 h	1 (AE)	35-28	Underpowered
Rebecca RC ¹²	R	Single	383	Not reported	≥ 10 RBC in 24 h	Severe TBI	24 h	1 (AE)	95-45-25-20	Did not include measures of acidosis and coagulopathy

¹ Indicates high plasma:RBC ratio was associated with survival.
² Indicates high plasma:RBC ratio was not associated with survival.
³ If study reported for patients with and without massive transfusion as defined by authors only information and results for massive transfusion population reported.
⁴ Abbreviations: Multi, multicenter; MT, massive transfusion; RBC, red blood cell units; ED, Emergency Department; OR, operating room; all, all-cause; results with logistic regression; TBI, traumatic brain injury; R, retrospective; P, prospective; RCTD, retrospective with prospectively collected data.
⁵ Indicates use US Military facility that had two high groups of patients rather than a 1:1 with medium ratio and another 1:1.
⁶ Exclusion of patients who died in the ED was not published but was confirmed by authors.

The Journal of TRAUMA® Injury, Infection, and Critical Care

The Ratio of Blood Products Transfused Affects Mortality in Patients Receiving Massive Transfusions at a Combat Support Hospital

Matthew A. Borgman, MD, Philip C. Spinella, MD, Jeremy G. Perkins, MD, Kurt W. Grathwohl, MD, Thomas Repine, MD, Alec C. Beckley, MD, James Sebesta, MD, Donald Jenkins, MD, Charles E. Wade, PhD, and John B. Holcomb, MD

Background: Patients with severe traumatic injuries often present with coagulopathy and require massive transfusion. The risk of death from hemorrhagic shock increases in this population. To treat the coagulopathy of trauma, some have suggested early, aggressive correction using a 1:1 ratio of plasma to red blood cell (RBC) units.

Methods: We performed a retrospective chart review of 246 patients at a US Army combat support hospital, each of who received a massive transfusion (≥10 units of RBCs in 24 hours). Three groups of patients were constructed according to the plasma to RBC ratio transfused during massive transfusion. Mortality rates and the cause of death were compared among groups.

Results: For the low ratio group the plasma to RBC median ratio was 1:3 (interquartile range, 0.12-1.5), for the medium ratio group, 1:2.5 (interquartile range, 1.0-3.0-12.3), and for the high ratio group, 1:1.4 (interquartile range, 1.17-11.2) ($p < 0.001$). Median Injury Severity Score (ISS) was 18 for all groups (interquartile range, 14-25). For low, medium, and high plasma to RBC ratios, overall mortality rates were 65%, 34%, and 19%, ($p < 0.001$), and hemorrhage mortality rates were 92.5%, 78%, and 37%, respectively, ($p < 0.001$). Upon logistic regression, plasma to RBC ratio was independently associated with survival (odds ratio 8.6, 95% confidence interval 2.1-35.2).

Conclusions: In patients with combat-related trauma requiring massive transfusion, a high 1:1.4 plasma to RBC ratio is independently associated with improved survival to hospital discharge, primarily by decreasing death from hemorrhage. For practical purposes, massive transfusion protocols should utilize a 1:1 ratio of plasma to RBCs for all patients who are hypocoagulable with traumatic injuries.

Key Words: blood components, Fresh frozen plasma, Trauma, Coagulopathy.

J Trauma 2007;63:805-813.

Borgman MA, et. al.: Study Design

- Retrospective study of patients with severe traumatic injuries requiring massive transfusion at a combat support hospital
- Objective: to determine whether the ratio of plasma to RBCs transfused would affect survival by decreasing death from hemorrhage.
- Data obtained from the Joint Theater Trauma Registry (JTTR) maintained at the US Army Institute of Surgical Research (USAISR), at Ft. Sam Houston, TX

Borgman, et. al.: Background

- Historically, whole blood (WB) used for massive trauma patients
- By late 1980s, component therapy (CT) had replaced WB therapy.
- Primary purpose of CT: optimal resource utilization/reduce infection disease transmission
- MT techniques extrapolated from elective surgery; lack of proof of the efficacy.
- Earlier resuscitation strategies:
 - Crystalloid in the field; RBCs for ongoing bleeding
 - FFP when PT or PTT 1.5X normal; or after 10 u PRBCs
 - Normal ratios around 1:4 PRBC:FFP
 - Platelets infused when PLT < 50-100K

Borgman, et. al.: Results

- Nov 2003 – Sep 2005 (23 mos); 5293 pts admitted to CSH in Baghdad
- JTTR identified 246 pts (4.6%) who received massive transfusion
 - 232 of 246 (94%) were from penetrating injuries
 - Median ISS = 18
 - Median stay at CSH = 2 days
 - Overall mortality = 28%

Borgman, et. al.: Results

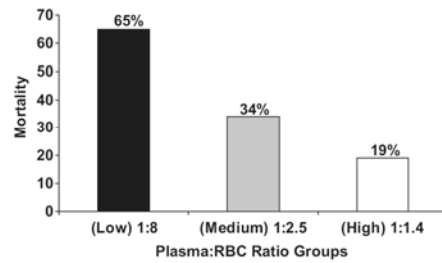
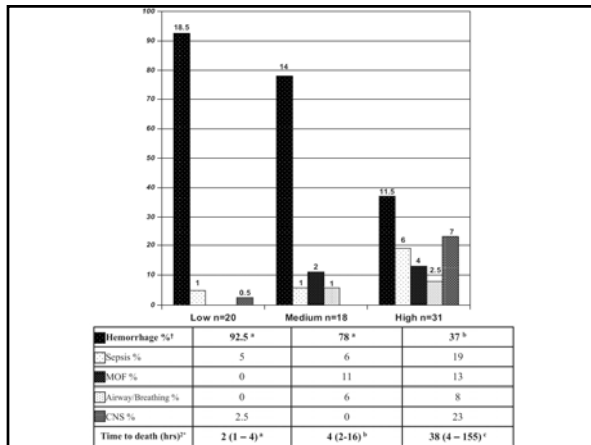


Fig. 1. Percentage mortality associated with low, medium, and high plasma to RBC ratios transfused at admission. Ratios are median ratios per group and include units of fresh whole blood counted both as plasma and RBCs.



Borgman, et. al.: Conclusion

- Higher plasma:RBC ratio independently associated with decreasing early death from hemorrhage
- Rate of crystalloid and blood product transfusion also decreased in high ratio group.
- Relationship between high plasma:RBC ratio and lower mortality preserved in alternative analysis independently excluding thoracic trauma, head trauma, whole blood and rFVIIa.
- In September 2004, guideline instituted to US Combat Support Hospitals supporting early use of 1:1:1 plasma:RBC:PLT ratios for patients at high risk of requiring a massive transfusion.
- “We suggest that the empiric ratio of plasma to RBC should approximate 1:1 for patients with traumatic injuries requiring massive transfusions.”

Postinjury Life Threatening Coagulopathy: Is 1:1 Fresh Frozen Plasma: Packed Red Blood Cells the Answer?

Jeffrey L. Kashuk, MD, Ernest E. Moore, MD, Jeffrey L. Johnson, MD, James Haenel, RRT, Michael Wilson, MD, John B. Moore, MD, Clay Cothren, MD, Walter L. Biffl, MD, Anirban Banerjee, PhD, and Angela Sautai, MD, PhD

Background: Recent military experience suggests that immediate 1:1 ratio of plasma:RBC (FFP:PRBC) may be beneficial for coagulopathy. We evaluated the effect of FFP:PRBC 1:1 on mortality in 133 patients who received >10 units RBC in 6 hours on 1:1 Coagulopathy (international normalized ratio [INR] >1.5 at 6 hours), controlling for our previously described risk factors predictive of coagulopathy, as well as RBC, FFP, and platelet administration. (2) Death (controlling for all variables plus age, crystalloids per 24 hours, INR >1.5 at 6 hours).

Results: Overall mortality was 56%; 80% died from acute blood loss in the operating room. Over 80% of the RBC transfusions were completed in the first 6 hours (Median RBC: 18 units) Median FFP:RBC: survivors, 1:2; nonsurvivors: 1:4 (p < 0.001). INR >1.5 at 6 hours occurred in 36 (23%); 51% died. Regarding mortality, logistic regression showed significant variables (p < 0.05) included: RBC per 6 hours (OR = 1.248, 95% CI: 1.057-1.425), INR at 6 hours >1.5 (OR = 10.208, 95% CI: 1.957-53.255), ED temperature <34°C (OR = 15.491, 95% CI 1.516-174.96), and age >55 years (OR = 20.531, CI: 5.315-300.677). The adjusted OR for FFP:RBC ratio including the quadratic term was found to follow a U-shaped association (quadratic term estimate 0.6737 ± 0.0345, p = 0.0189).

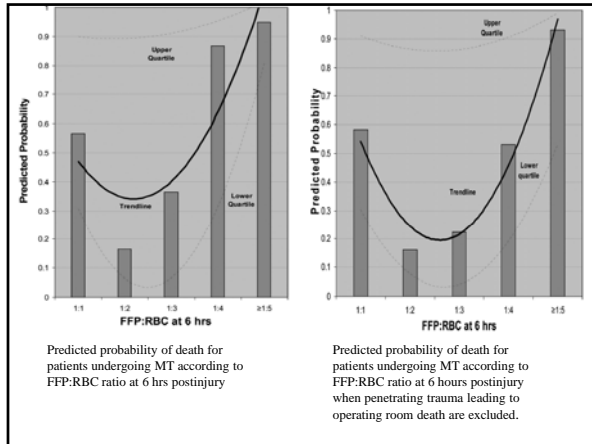
Conclusion: Although our data suggest that 1:1 FFP:RBC reduced coagulopathy, this did not translate into a survival benefit. Our findings indicate that the relationship between coagulopathy and mortality is more complex, and further clinical investigation is necessary before recommending routine 1:1 in the coagulating trauma patient.

Key Words: Postinjury, Coagulopathy, Plasma, Transfusion.

J Trauma. 2008;65:204-211

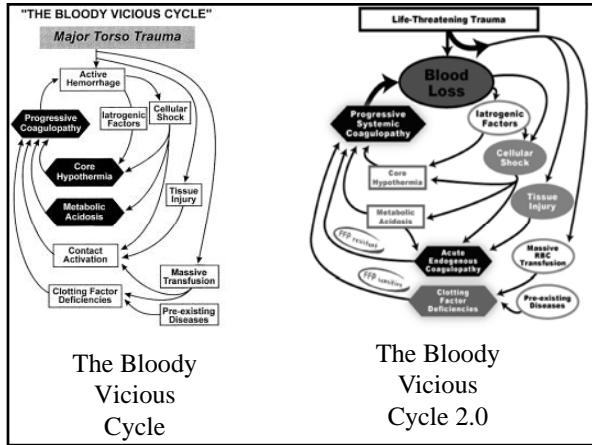
Kashuk, et. al.: Study Design

- Purpose: Review recent 5 year massive transfusion practices for acutely injured patients to evaluate the impact of FFP:RBC ratio on coagulopathy and mortality
- Retrospective analysis of Trauma and Transfusion Registry in level 1 trauma center from 2001-2006
- 133 trauma patients received > 10 units of PRBCs within 6 hours of admission
- Excluded were severe head injury judged to be the cause of death



Kashuk, et. al.: Conclusion

- Data suggest that 1:1 FFP:RBC ratio did reduce coagulopathy, this did not translate into a survival benefit.
- The relationship between coagulopathy and mortality is more complex.
- Further clinical investigation is necessary before recommending routine 1:1 in the exsanguinating trauma patient.



The Journal of TRAUMA Injury, Infection, and Critical Care

Warm Fresh Whole Blood Is Independently Associated With Improved Survival for Patients With Combat-Related Traumatic Injuries

Philip C. Spinella, MD, Jeremy G. Perkins, MD, Kurt W. Grathwohl, MD, Alec C. Beckley, MD, and John R. Holcomb, MD

Background: Increased understanding of the pathophysiology of the acute coagulopathy of trauma has led many to question the current transfusion approach to hemorrhagic shock. We hypothesized that warm fresh whole blood (WFWB) transfusion would be associated with improved survival in patients with trauma compared with those transfused only stored component therapy (CT).

Methods: We retrospectively studied US Military combat casualty patients transfused ≥ 1 unit of red blood cells (RBCs). The following two groups of patients were compared: (1) WFWB, who were transfused WFWB, RBCs, and plasma but not apheresis platelets and (2) CT, who were transfused RBC, plasma, and apheresis platelets but not WFWB. The primary outcomes were 24-hour and 30-day survival.

Results: Of 354 patients analyzed there were 100 in the WFWB and 254 in the CT group. Patients in both groups had similar severity of injury determined by admission eye, verbal, and motor Glasgow Coma Score, base deficit, international normalized ratio, hemoglobin, systolic blood pressure, and injury severity score. Both 24-hour and 30-day survival were higher in the WFWB cohort compared with CT patients, 96 of 100 (96%) versus 223 of 254 (88%), ($p = 0.018$) and 82% to 82%, ($p = 0.002$), respectively. An increased amount (825 mL) of additives and anticoagulants were administered to the CT compared with the WFWB group, ($p < 0.001$). Upon multivariate logistic regression the use of WFWB and the volume of WFWB transfused was independently associated with improved 30-day survival.

Conclusions: In patients with trauma with hemorrhagic shock, resuscitation strategies that include WFWB may improve 30-day survival, and may be a result of less anticoagulants and additives with WFWB use in this population.

Key words: Whole blood, Transfusion, Mortality, Survival, Combat.

J Trauma. 2009;66:569-576.



Spinella PC, et. al: Methods

- 354 patients met inclusion criteria, divided into two groups
 - WFWB group: transfused WFWB, RBCs, and plasma but not apheresis platelets (aPLT) (100 pts; 28%)
 - CT (Component Therapy) group: transfused RBC, plasma, and aPLT but not WFWB (254 patients; 72%)
- Primary outcomes were 24 hour and 30 day survival
- All blood products measured at first 24 hours
- Patients in both groups had similar severity of injury determined by GCS, base deficit, INR, Hgb, SBP, and ISS.

Spinella PC, et. al: Results

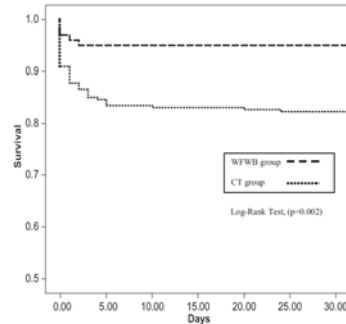


Fig. 1. Kaplan-Meier curve of 30-day survival according to study group.

Spinella PC, et. al: Results

Table 7 Multivariate Logistic Regression Results With Blood Product Amount for 30-d Survival

Variables	OR (95.0% C.I.)	p Value
WFWB (U)	2.15 (1.21–3.8)	0.016
RBC (U)	0.91 (0.85–0.97)	0.003
Plasma (U)	1.09 (1.02–1.18)	0.019
Base deficit	0.91 (0.84–0.97)	0.002
GCS eyes (normal)	3.8 (1.4–10.2)	0.009
ISS	0.94 (0.91–0.98)	0.001

AUC (95% CI) for the logistic regression was 0.9 (0.86–0.95).

Spinella PC, et. al: Discussion

- “It is our belief that WFWB is more efficient than stored CT at correcting coagulopathy and shock in this population...”
- WFWB is more concentrated, better suited product than CT to prevent/correct shock and O2 debt in critically ill patient.
- Minimizes adverse effects of transfusion of “storage lesion” of older RBCs.
- WFWB group received less anticoagulants and additives than CT group.

Spinella PC, et. al: downside of WFWB:

- Potential that transfusion of increased amounts of WBCs promotes inflammation through mechanisms such as transfusion-associated microchimerism (TA-MC)
- Increased incidence of renal failure, DVT, and ARDS among WFWB group
- Increased risk of Transfusion Transmitted Infectious Diseases (TTDs)

What to look for in Trauma Anesthesia

- rFVIIa: further refinement regarding ideal setting for use in trauma
- Etomidate: still the ideal induction agent in the setting of trauma?
- HBOCs: revolutionary innovation vs. dead end technology
- Prehospital treatment: less IV fluid, more tourniquet use, granule refinement, better bandagesHB live
- POC coagulation assays (rTEG): perhaps the best method for guiding component therapy

Summary