Managing Hemostasis in Trauma

Acute Coagulopathy of Trauma/Shock

NovoSeven® Efficacy and Risk
Cyclokapron (tranexamic acid)

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Death by Trauma: Statistics

- Unintended or intentional injury are the most common cause of death in N Americans age 1–45
  - 93,000/year in the USA
  - 3,000,000 worldwide, but exceeded by AIDS deaths
- 50% of trauma deaths are caused by neurological displacement and occur before reaching hospital
- 20,000 die in hospital of exsanguination within 48 hours
  - 30–35% of blood loss with uncompensated shock is fatal
  - 3–4,000 of US hemorrhage deaths are preventable
- Coagulopathy, failure to achieve hemostasis


24-YO ♂, GSW in ED

A 24-YO male arrived in the ED with a gunshot wound causing massive abdominal trauma. He had been given three units of Dextran® in transit to achieve fluid resuscitation but was hemorrhaging. ED personnel ordered and administered four RBC units. Upon the second RBC four-unit batch order the transfusion service director recommended one plasma and one pheresis platelet concentrate. After 8 RBCs, 1 plasma, and 1 platelet, still bleeding, labs were:

- PT: 20.8 s (Mean of RI 12.9); PTT: 82.5 s (MRI 30.1)
- FG: 130 mg/dL (225–498 mg/dL); PLTs: 70,000/mcL

24-YO ♀, GSW in ED

In surgery, major vessels were tied, but the field was obscured by microvascular bleeds. The patient went into shock and expired.

Thanks to Margaret Fritsma, Mary Anne Krupsky, Michelle Brown, Birmingham, AL and Jose De Jesus, Tuscaloosa, AL for information on which this case is based.

American Society of Anesthesiologists Surgical Practice Guidelines: RBCs

- Monitor BP, pulse, ABG (pH, O₂ sat), urine output, EKG when feasible
- Monitor physical blood loss
- Transfuse when HGB <6 g/dL in young, healthy patient
- Do not transfuse when HGB >10 g/dL
- Transfuse based on acuity and clinical history when HGB 6–10 g/dL
  - O₂ sat, tissue ischemia, bleeding rate, IV volume replacement, evidence for coagulopathy
- Autotransfuse (recovery) when feasible
Managing Hemostasis in Trauma

American Society of Anesthesiologists
Practice Guidelines: Coagulopathy

- Assess surgical field for microvascular bleeding
  - Suction canisters, surgical sponges, surgical drains
- Platelet concentrate transfusion
  - No platelets if count is >100,000/mcL
  - “Usually” give platelets if <50,000/mcL, unless...
    - Limited blood loss is anticipated based on type of surgery
    - Thrombocytopenia is due to HIT, ITP, or TTP, where platelets may be ineffective
  - From 50–100,000/mcL, use platelets if...
    - Potential of bleeding into confined space such as brain or eye
    - Aspirin, clopidogrel, cardiopulmonary bypass, platelet disorder


Current Typical Approach to ACOTS

American Society of Anesthesiologists
Practice Guidelines: Coagulopathy

- Do not use plasma only to augment volume, use colloid plasma expanders
- Give plasma if microvascular bleeding...
  - And PT >1.5X normal (“normal” is undefined),
  - Or PTT >2X normal,
  - Or when transfused with >1 blood volume (~70 mL/kg),
  - Or need for urgent reversal of warfarin therapy,
  - Or known factor deficiency & concentrate is unavailable,
  - Or heparin resistance (antithrombin deficiency).
- Dosage is 10–15 mL plasma/kg to achieve ≥30% factor concentration
  - Or 5–8 mL/kg if only for warfarin reversal


Current Typical Approach to ACOTS

American Society of Anesthesiologists
Practice Guidelines: Coagulopathy

- CRYO when there is microvascular bleeding and...
  - Fibrinogen <100 mg/dL or documented deficiency,
  - Or massive transfusions without opportunity to determine fibrinogen level
  - CRYO delivers 150–250 mg fibrinogen
  - Consider recombinant activated factor VII (NovoSeven, rFVIIa) when RBCs, PLTs, plasma and CRYO fail


Current Typical Approach to ACOTS

Massive Trauma With Hemorrhagic Shock

- Systolic <110 mm Hg
- Pulse >105
- pH <7.25
- HCT <32%
- HGB <10 g/dL
- INR >1.5 (Is INR the correct measure?)


Massive Tx requirement is likely in young, healthy combat casualties when...

RBC/Plasma 1:1?

- USA hospital in Baghdad Green Zone
  - Retrospective w/o controls but extensive, accurate data
  - Tx >2000 wounded, massively Tx >600 wounded
- Ratio and results
  - Receiving <1 plasma for every 4 RBCs: 65% mortality
    - Confounding data: soldiers who received >10 RBCs but died before plasma could thaw are counted in this arm
  - Receiving 2 plasma for every 3 RBCs: 19% mortality
    - Surgeons report less bleeding and edema
  - Now implementing 1:1 plasma/RBC Rx
- Anticipated adverse effects; none recorded
  - Plasma supply (yes), TRALI, anaphylaxis, ARDS, MOF, thrombosis

Managing Hemostasis in Trauma

3.31.11

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The Fritsma Factor

Acute Coagulopathy of Trauma-Shock (ACOTS)

- Hypoperfusion (shock)
- Hypothermia (shock)
- Tissue factor activation
- Acidosis (shock)
- Platelet activation
- Surgical damage
- Hemodilution by fluid resuscitation

The Fritsma Factor

Acute Coagulopathy of Trauma—Shock (ACOTS)

- Acidosis (shock)
- Hypothermia (shock)
- Hemodilution by fluid resuscitation
- Hypoperfusion (shock)

The Fritsma Factor

Surgical damage

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Inflammation

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Tissue factor activation

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Platelet activation

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Protein C activation

The Fritsma Factor

Hyperfibrinolysis

The Fritsma Factor

RBCs

The Fritsma Factor


The Fritsma Factor

Hyperfibrinolysis

The Fritsma Factor

Protein C activation

The Fritsma Factor

Coagulation Pathway

The Fritsma Factor

Intrinsic

The Fritsma Factor

Extrinsic

The Fritsma Factor

Common

The Fritsma Factor

Pre-K

The Fritsma Factor

Fibrinogen

The Fritsma Factor

Fibrin Polymer

The Fritsma Factor

Crosslinked Fibrin

The Fritsma Factor

The Fritsma Factor

Injury Severity Score (ISS)

Region | Description (Examples) | Injury Score (1–6) | Highest 3 Squared |
--- | --- | --- | --- |
Head & neck | Cerebral contusion | 3 (Serious) | 9 |
Face | Scratches | 1 (Minor) |
Chest | Sucking wound | 4 (Severe) | 16 |
Abdomen | Liver contusion | 2 (Moderate) | 5 (Critical) | 25 |
Extremity | Fractured femur | 3 (Serious) |
Total ISS | | | 50 |

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Coagulopathy in Trauma

ISS & Coagulopathy n = 1088 % Coagulopathy by Lab Assay

Injury severity score (ISS) >15; median 20 57.7% | Coagulopathy at Admission % Mortality

Yes (24.4%) | 46%

No | 10.9%

Overall mortality | 19.5%

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Coagulopathy defined prior to & independent of fluid replacement as: PT >16s, 16.3%; PTT >60s, 24.4%; or thrombin time >15s, 14.2%


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Probability of Life-threatening Coagulopathy

Condition (n = 58, >10 RBCs) | Percent Coagulopathy

Injury severity score (ISS) >25 alone | 10%

ISS >25 & systolic BP <70 mm Hg | 39%

ISS >25 & body temp <34°C | 49%

ISS >25 & pH <7.10 | 58%

ISS >25 & SBP <70 mm Hg; body temp <34°C | 85%

ISS >25 & SBP <70 mm Hg; temp <34°C; pH <7.10 | 98%

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Life-threatening coagulopathy is arbitrarily defined as PT and PTT >2X mean of reference interval


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PT and PTT Predict Mortality

- Review of 7638 level I trauma admissions
- Initial PT >14s: 28% of admissions
  - 6.3% of patients with PT <14s died
  - 19.3% of patients with PT >14s died
  - Independent mortality increase 35%; OR, 3.6; p <0.0001
    - When controlling for age, ISS, BP, HCT, pH, and head injury
- Initial PTT >34s: 8% of admissions
  - Independent mortality increase 326%; OR 7.8; p <0.001

## Definition and “Drivers” of ACOTS

- Retrospective cohort study
  - 3646 trauma patients at 5 international trauma centers
- Prothrombin time ratio >1.2
  - Mortality 22.7% Vs. 7.0%, \( p < 0.001 \)
  - RBCs 3.5 Vs. 1.2 units, \( p < 0.001 \)
  - Plasma 2.1 Vs. 0.8 units, \( p < 0.001 \)
- ACOTS defined as PTR >1.2 correlates with ISS and shock
- Confirmed using rat model (not described)


## Coagulopathy

- PTR rise depends upon both ISS and hypoperfusion
- Mortality mirrors PTR as it also depends upon both ISS and hypoperfusion
- Base deficit (mmol/L) mirrors hypotension (shock)

## Recombinant Activated Factor VII

- Pre-1980 (and still available)
  - Prothrombin complex concentrates (PCC) extracted from human plasma using \( \text{BaSO}_4 \) absorption: Proplex®
  - Factors II, VII, IX, and X, once used for IX deficiency patients
  - Activated PCC for FVIII or FIX deficiency with inhibitors
  - FEIBA FH®
    - Variant efficacy traced to FVIIa activity
- 1980: Extract FVIIa from human plasma
  - Kisiel, Broze
- 1983: Compassionate use in two humans
- 1988: Novo Nordisk®, Bagsvaerd, Denmark, undertook to synthesize rFVIIa
  - March 25, 1999: FDA releases NovoSeven® rFVIIa


## FEIBA FH Dosages

- Activated prothrombin complex concentrate
  - Activated II (thrombin), VII, IX, and X

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint bleeding</td>
<td>50 units/kg every 12 h</td>
</tr>
<tr>
<td>Mucous membrane bleeding</td>
<td>50 units/kg every 6 h</td>
</tr>
<tr>
<td>Muscle bleeding</td>
<td>100 units/kg every 12 h</td>
</tr>
</tbody>
</table>

To avoid DIC, FEIBA FH dose may not exceed 200 units/kg in 24 hours and infusion rate may not exceed 2 units/kg/minute.

There is no test to monitor FEIBA. The patient’s clinical response, e.g., bleeding or hematoma size, is the only guide.

Cost $0.50/unit, single Rx for a 70 kg patient is $1750

## rFVIIa; NovoSeven

- Secreted from baby hamster kidney cells, proteolytically converted to two-chain active form
- Limitation: \( \gamma \)-carboxylation of 2/3 of glutamic acids at amino terminus
  - Seems to be enough \( \gamma \)-carboxylated GLUs
  - Requires compressed \( \gamma \)-glutamyl carboxylase
  - Requires vitamin K

\[ \text{rFVIIa} \]

\[ \text{NH}_2 \]

\[ \text{12 GLU molecules} \]

\[ \rightarrow 8 \text{ become GLA} \]
Physiology of rFVIIa & Tissue Factor

- rFVIIa binds TF of injured vessels, activating FX; FXa activates IIa; generates fibrin
- rFVIIa activates platelets directly through thrombin receptors and triggers primary coagulation even in Glanzmann thrombasthenia
- rFVIIa activates thrombin activatable fibrinolysis inhibitor (TAFI), simultaneously reduces fibrinolysis
- rFVIIa hemostatic action is localized by TF
  - FEIBA functions systemically
  - DIC risk is negligible


Coagulation Pathway

Platelet Receptors (and 50 more)

- Fg/VWF receptor: GP Ib/IIa (Glanzmann)
- PAR
- FVIII receptor: GP Ib/IX/V, CD 42 (Bernard-Soulier)
- Thrombin receptor: protease activatable receptor (PAR)
- VWF receptor: GP Ib/IIa

Fibrinolysis

- Free Plasmin
- α2-antiplasmin
- TPA
- Bound Plasmin
- PAI-1
- TAFI
- FDPs, D-dimer

Summary: ACOTS

- Massive Tx; observe for hypothermia, acidosis (base deficit), coagulopathy
- Surgery use warm fluids, warmed EBL, gamma-irradiation, observe for microvascular bleeding
- Coagulopathy RBC, PLT, Plasma 1:1:1, INR, PT, aPTT
- Hypothermia remove wet clothing, cover with blanket, peripheral irrigation
- Acidosis check resuscitation, normal saline, correct base deficit


rFVIIa 3/25/99 FDA Indications

- Bleeding episode Rx in hemophilia A or B with inhibitors or in acquired hemophilia
- Bleeding prevention in invasive procedures in hemophilia A or B with inhibitors or acquired hemophilia
- Bleeding Rx in congenital FVII deficiency
- Bleeding prevention in invasive procedures in congenital FVII deficiency

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rFVIIa Dosages Cleared by FDA

<table>
<thead>
<tr>
<th>Cleared Indication</th>
<th>IV Bolus Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia A or B or acquired hemophilia with inhibitor</td>
<td>90 mcg/kg every 2 h</td>
</tr>
<tr>
<td>• Bleeding episode</td>
<td>until hemostasis is</td>
</tr>
<tr>
<td></td>
<td>achieved</td>
</tr>
<tr>
<td>Hemophilia A or B or acquired</td>
<td>90 mcg/kg immediately</td>
</tr>
<tr>
<td></td>
<td>before and every 2 h</td>
</tr>
<tr>
<td></td>
<td>during surgery</td>
</tr>
<tr>
<td>Post-surgery</td>
<td>90 mcg/kg every 2 h</td>
</tr>
<tr>
<td>• minor</td>
<td>for 48 h, then every</td>
</tr>
<tr>
<td></td>
<td>2–6 h until healed</td>
</tr>
<tr>
<td>Post-surgery</td>
<td>90 mcg/kg every 2 h</td>
</tr>
<tr>
<td>• major</td>
<td>for 3 d, then every 2</td>
</tr>
<tr>
<td></td>
<td>h until healed</td>
</tr>
<tr>
<td>Congenital FVII deficiency—bleeding episode or surgery</td>
<td>15–30 mcg/kg every 4</td>
</tr>
<tr>
<td></td>
<td>– 6 h until healed</td>
</tr>
<tr>
<td>Acquired hemophilia—bleeding episode or surgery</td>
<td>70–90 mcg/kg every 2–3</td>
</tr>
<tr>
<td></td>
<td>h until hemostasis is</td>
</tr>
<tr>
<td></td>
<td>achieved</td>
</tr>
<tr>
<td>Cost $1.00/mcg, single Rx for a 70 kg patient is $6300</td>
<td></td>
</tr>
</tbody>
</table>

Off-label Applications for NovoSeven

- Cardiac, thoracic, aortic and spinal surgery; hepatic resection; hysterectomy or postpartum bleeding
- Severe multiple trauma
- Non-traumatic intracranial hemorrhage if <4 hours from onset
- Reversal of antithrombotic (warfarin) overdose

Off-label Guidelines for NovoSeven

- Evaluate underlying disorder
- Evaluate salvageability of the patient
- Ensure no inherent thrombophilia, prior AMI or stroke
- Exhaust current treatment options
  - RBCs, plasma, PLTs, CRYO
- Document amount of blood products used
- Ensure pH >7.25

Generalized Off-label Guidelines for NovoSeven

- Always offer rFVIIa when bleeding continues after conventional Tx therapy
  - RBC, plasma, platelets, and CRYO
  - rFVIIa doesn’t work when coagulation factors <30%
  - 40–90 mcg/kg in adults for all emergent scenarios
- Contraindicated in previous thrombosis
  - Stroke: ensure it is intracranial hemorrhage
  - Assume no thrombosis in young trauma victims
- 20–40 mcg/kg in non-emergent warfarin reversal

Spinella: Iraq Combat Trauma

- Retrospective case-control study of 124 severe Iraq combat trauma patients
  - >10 units RBCs/24 h
- Determine if rFVIIa reduces 24 h and 30 d mortality
- Determine association of rFVIIa with severe VTE


Off Label Use in Trauma: 2005

- Israeli soldier with bleeding rescued by rFVIIa
- Approved by USA surgeon general for battlefield
- Case reports of efficacy and research protocols by Col. John B. Holcomb, MD
  - Commander of the US Army Institute of Surgical Research, Ft Sam Houston, TX, and Trauma Consultant for The Army Surgeon General

Managing Hemostasis in Trauma

Spinella: Mortality Rate in Iraq

<table>
<thead>
<tr>
<th>Total Mortality Rate</th>
<th>12 h</th>
<th>24 h (cumulative)</th>
<th>30 d (cumulative)</th>
<th>Thromboembolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>62</td>
<td>71</td>
<td>49</td>
<td>0</td>
</tr>
<tr>
<td>rFVIIa</td>
<td>29</td>
<td>36</td>
<td>38</td>
<td>0</td>
</tr>
</tbody>
</table>

12 h: 49%, 24 h: 65%, 30 d: 64%

37 patients died from hemorrhage

Harrison: General Trauma

- Prospective study of rFVIIa-treated trauma patients matched to historic controls
- Mortality rates: 41% in rFVIIa, 40% in controls (NS)
- Thromboemboli: 6.9% in rFVIIa, 19.7% in controls; (P=0.03)

Transfusion

<table>
<thead>
<tr>
<th>RBC (units)</th>
<th>Plasma (units)</th>
<th>PLT (5-pack units)</th>
<th>Cryo (5-pack units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>72 Controls</td>
<td>29 Cases</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For Patients Alive at 48 Hours

<table>
<thead>
<tr>
<th>Median RBC Units</th>
<th>Blunt Trauma</th>
<th>Penetrating Trauma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>rFVIIa</td>
<td>Placebo</td>
</tr>
<tr>
<td>7.5 (n=72)</td>
<td>7.0 (n=52)</td>
<td>4.2 (n=52)</td>
</tr>
</tbody>
</table>

Holcomb: Tx Requirements: 48 Hours After First Dose of rFVIIa

<table>
<thead>
<tr>
<th>Placebo</th>
<th>rFVIIa</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC (units)</td>
<td>66.6</td>
<td>48.2</td>
</tr>
<tr>
<td>Plasma (mL)</td>
<td>1400</td>
<td>630</td>
</tr>
<tr>
<td>PLT (mL)</td>
<td>620</td>
<td>505</td>
</tr>
</tbody>
</table>

- Incidence of MOF or ARDS was 20% for placebo, 3% for rFVIIa, P=.004
- Incidence of thromboembolic events was 4% for placebo and 3% for rFVIIa, P=1.00

FDA Reports Thromboembolic Events

Divs. of Epidemiology and Hematology collected adverse event data 3/25/99–12/31/04, all US and non-US patients including post-licensure clinical trials

For Patients Alive at 48 Hours

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>rFVIIa</td>
<td>Placebo</td>
</tr>
<tr>
<td>3.4 (n=3)</td>
<td>2.3 (n=3)</td>
<td>3.5 (n=4)</td>
</tr>
</tbody>
</table>


FDA Reports Thromboembolic Events

168 reports: 183 thrombotic events, 52 deaths

FDA factors in US Food and Drug Administration
### Thrombotic Event Sites

<table>
<thead>
<tr>
<th>Site</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>39 (21.3%)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>34 (18.6%)</td>
</tr>
<tr>
<td>Peripheral artery occlusion</td>
<td>26 (14.2%)</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>42 (22.9%)</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>32 (17.5%)</td>
</tr>
<tr>
<td>Occluded line</td>
<td>10 (5.5%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>183 (100%)</td>
</tr>
</tbody>
</table>

Patients in 5-year survey: ~10,700
Rate of thrombotic events: 0.017%

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### Novo Nordisk Phase 2 Trial

- Multicenter prospective randomized double-blind placebo-controlled trial evaluated effect of rFVIIa on RBC transfusion requirements in patients with blunt or penetrating trauma
- **277 patients, 143 blunt, 134 penetrating**
  - Criteria: required 6 RBC units within 6 hours of admission
  - Placebo or rFVIIa at 0 h (200 mcg/kg), 1 h (100 mcg/kg), and 3 h (100 mcg/kg)
- **Adverse events:** adult respiratory distress syndrome (ARDS), multi-organ failure (MOF) and thromboembolic events (TE)


### rFVIIa Phase III Trial Withdrawal


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### Baltimore Sun, May 16, 2010

**Federal agents probing Army’s use of trauma drug**

**Critical Investigation looking at military’s use of blood clotting ingredients for treating war casualties**

May 16, 2010 | By Robert Lyle, The Baltimore Sun

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### Tranexamic Acid (Cyclokapron) Rx

- **Synthetic lysine blocks plasminogen binding sites**
  - Cyclohexane carboxylic acid
- **Reduces Tx requirements in surgery without raising mortality**
- **Aprotinin (trypsin inhibitor, anti-fibrinolytic) ineffective, withdrawn in 2008**

Tranexamic Acid Death by Cause

<table>
<thead>
<tr>
<th>CRASH-2</th>
<th>TXA</th>
<th>Placebo</th>
<th>RR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 10060</td>
<td>n = 10067</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any cause of death</td>
<td>1463 (14.5%)</td>
<td>1613 (16%)</td>
<td>0.91</td>
<td>0.0035</td>
</tr>
<tr>
<td>Bleeding death</td>
<td>489 (4.9%)</td>
<td>574 (5.7%)</td>
<td>0.85</td>
<td>0.0077</td>
</tr>
<tr>
<td>Vascular occlusion death</td>
<td>33 (0.3%)</td>
<td>48 (0.5%)</td>
<td>0.69</td>
<td>0.096</td>
</tr>
<tr>
<td>No dependency symptoms</td>
<td>1463 (14.7%)</td>
<td>1334 (13.3%)</td>
<td>1.11</td>
<td>0.0023</td>
</tr>
</tbody>
</table>

- No significant differences:
  - MI, stroke, PE, DVT, blood products, surgery

All-cause Mortality by Subgroups

<table>
<thead>
<tr>
<th>Tourniquet Applied</th>
<th>Shock Absent</th>
<th>Shock Present</th>
<th>Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-hospital</td>
<td>171/17 (91%)</td>
<td>1/5 (17%)</td>
<td>171/22</td>
</tr>
<tr>
<td>In ED</td>
<td>29/5 (85%)</td>
<td>0/4 (0%)</td>
<td>29/9</td>
</tr>
<tr>
<td>Sum</td>
<td>200/22</td>
<td>1/9</td>
<td>201/31</td>
</tr>
</tbody>
</table>

Alive/Dead: Tourniquet use in absence of shock Vs not, p=0.4x10^-8; pre-hospital Vs ED tourniquet, p=0.06

Survival in Afghanistan

- January 7, 2011
- Speedy evacuation
- Tourniquets
- Cyclokapron (tranexamic acid)
- NovoSeven (rVIIa)