Recombinant Factor VIIa in Trauma: Use or Abuse?

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Disclosure

• Recombinant FVIIa has not been approved by the FDA for use in trauma patients.
• Dr. Knudson has received grant support from NovoNordisk Pharmaceuticals to collect case studies on trauma patients receiving FVIIa.

Death In The Operating Room: Hoyt/Knudson 1996

• Multicenter study: 537 OR deaths
• Average BP on arrival: 60 mm HG
• Best Temp: 32.2 C
• Cause of death: bleeding (82%)

Hypotension + Hypoperfusion = Coagulopathy

• Blood collected: on arrival at SFGH
• No time for salt water drowning!
• Early coagulopathy predicts mortality

Brohi, Cohen: Annals Surgery 2007
**Triangle Of Death From Hemorrhage**

- pH < 7.1
- BE < -12
- Ca++ < 0.9
- T° < 34°

**Triangle of Death**

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**Hemorrhage Control And Transfusion Practice**

- Massive transfusion → >10 units/24 hours
- Deaths from hemorrhage: 2-6 hours
- MT- 1-3% of civilian trauma patients
- Mortality: 20-50%

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**Recombinant Factor VII (rFVIIa)**

- Developed for Rx of bleeding: primary hemophilia with inhibitors*
- In Europe: approved for use in bleeding from acquired hemophilia
- Enhances hemostasis primarily at the site of injury without activating the systemic cascade

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**Coagulation Cascade: Traditional**

Intrinsic Pathway

Extrinsic Pathway

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*Novo Nordisk, Denmark*
Coagulation Cascade: Network

Trauma and rFVIIa

- 1999: First published successful case
- High-velocity GSW: military combat
- Traumatic coagulopathy-IVC injury

Kenet, Matinowitz Lancet

Novo Nordisk Trial 2001-2003

- Only randomized, prospective trial
- Placebo-controlled: traumatic shock

- Phase II; Multi-center; Multi-national

BACKGROUND

- One prospective randomized study*
- Reduction in units of blood transfused
- No mortality/morbidity benefit

* Boffard et al J Trauma 2005
Second study abandoned for futility
Factor VIIA and TBI

- Retrospective review: 63 TBI patients
- 29 received FVIIa: coagulopathy
- 34 treated with FFP
- Decreased time to intervention: FVIIa
- Mortality benefit: (33% vs. 52%)

MT/Factor VIIA/Combat Casualties

- 124 pts. with FVIIa and MT
- 75 with MT only
- Death from hemorrhage: 57% vs. 78%
- No difference in thrombotic complications

Adverse Events and FVIIa

- 431 AEs reported (2006)*
- 185 thromboembolic events
  - CVAs
  - MIs
  - PE
  - DVT
- 151/185: off label use

*O’Connell et al: JAMA

Trauma Transfusions and Recombinant FVIIa: An Analysis of 380 Patients

MM Knudson, MJ Cohen, R Reidy, S Jaeger, P Bacchetti, J Chengshi, CE Wade, JB Holcomb
A WTA Multi-Center Studies Group Initiative
INTRODUCTION

- rFVIIa: developed for hemophiliacs with acquired inhibitors
- Increasingly utilized “off-label” for acquired coagulopathy during surgery
- Wide application: civilian and military trauma
- Efficacy?
- Safety?

WTA Multi-Center Studies

- Very successful trauma research group
- Completed 27 multi-center studies*
- Approached by Novo Nordisk (NovoSeven)
- Design/Conduct: Case Registry Study
- Purpose: describe use of rFVIIa in U.S. trauma centers

*www.westerntraumaassociation.org

HYPOTHESIS

Identify the patients and describe the setting in which rFVIIa would be successful in reducing mortality from post-traumatic hemorrhage

METHODS

- Open to WTA and AAST participants
- Retrospective/prospective data collection
- Inclusive years: 2003-2008
- Web-based comprehensive registry
- Pass-word protected/user-friendly
- Assured data integrity/accuracy
RESULTS

• 716 patients from 21 trauma centers-rFVIIa
• Eliminated from the analysis:
  - isolated head injuries
  - pediatric patients
  - rFVIIa > 24 hours
  - doses < 40 mcg/kg
• 380 patients with transfusions/rFVIIa

Patients Receiving rFVIIa

• 70%: Blunt Injury
• Admit Temperature: 35.6 degrees
• Admit pH = 7.1
• Admit base deficit: 10.2
• Admit INR: 1.9
• Mean ISS: 34

RESULTS: rFVIIa Group

• Mean time from admit/first dose: 4.6 hrs.
• Range: 0.2-23 hours
• Average dose: 96.1 ug/kg
• 27%-second dose
• 6%-third dose

Most common location: OR

RBCS: 1ST 24 HOURS

<table>
<thead>
<tr>
<th>Number of units RBCs</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td></td>
<td></td>
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<tr>
<td>Median</td>
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</tbody>
</table>

Range 0-99 units

Range 0-120 units
Outcomes

- Mortality rate: 54.5%
- Death from hemorrhage: 39%
- Death from MOF: 16%

Predictors Of Death From Hemorrhage

- Admit PTT > 60 sec
- Admit PH < 7.2
- AIS ABD/Chest/Head ≥ 3
- Admit BP ≤ 90
- rFVIIa ≥ 4 units (late)

Response to rFVIIa

<table>
<thead>
<tr>
<th>Odds Ratios: 0 = Death/hemorrhage 1=Lived</th>
<th>pH ≥ 7.2</th>
<th>pH &lt; 7.2</th>
<th>Platelets ≥ 100</th>
<th>Platelets &lt; 100</th>
<th>BP &gt; 90</th>
<th>BP &lt; 90</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.14</td>
<td></td>
<td></td>
<td></td>
<td>0.42</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Thrombotic Complications

<table>
<thead>
<tr>
<th>Event</th>
<th>Number / % total survivors</th>
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<tbody>
<tr>
<td>DVT</td>
<td>26 / 9.9%</td>
</tr>
<tr>
<td>PE</td>
<td>6 / 2.3%</td>
</tr>
<tr>
<td>Acute MI</td>
<td>12 / 4.6%</td>
</tr>
<tr>
<td>Stroke</td>
<td>3 / 1.1%</td>
</tr>
</tbody>
</table>
LIMITATIONS

• Non-randomized, primarily retrospective
• Timing/dosing variations
• No direct proof of efficacy
• Biased against rFVIIa

CONCLUSIONS

• rFVIIa: limited benefit as currently utilized
• rFVIIa—likely to be most effective:
  - early in MT protocol
  - in absence of shock/acidosis
  - in presence of adequate platelets

rFVIIa and TBI

• 199 patients
• “Responders”: improved 2nd head CT

<table>
<thead>
<tr>
<th></th>
<th>Non-responders</th>
<th>Responders</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>141</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Mean AIS-head</td>
<td>4.34</td>
<td>4.15</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality</td>
<td>59.97%</td>
<td>21.74%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

POC Coagulation Monitoring

Thromboelastograph
(Haemoscope Corp.)

Sonoclot
(Sienco Inc.)
**Conclusion**

- Factor VIIa is expensive ($5,000)
- One whole blood transfusion ($5,000)
- Effects can be dramatic!
- Use is wisely as part of a MT protocol