Post-Traumatic Thromboembolism

Pathogenesis, Diagnosis and Prevention

M. Margaret Knudson, MD
"A study of protocols of 9,882 postmortem exams including death from injury...in the traumatic group embolisms were found in 61 cases (3.8%) and in the non-traumatic group in 222 cases (2.6%). Statistically, this appears to be a significant difference."

J.S. McCartney, 1934
Historical Perspectives

- 124 trauma patients: venograms
- Fracture patients: 35% venous thrombosis
- Thrombus found within 24 hours of injury
- Both injured/uninjured extremity
- 2/3rds with DVT-asymptomatic

Freeark et al, 1967
Pathophysiology: VTE

- Direct injury to endothelium
- As surgical incision is made:
  - veins remote from site dilate
  - Stasis/inflammation/thrombosis
Knudson’s Trauma Triad

- Multiple Transfusions
- Severe Injuries
- Paralysis
- Immobilization
- Venous trauma fractures
- Endothelial damage
- Hypercoagulability
- Stasis

Knudson’s Trauma Triad
INCIDENCE: OCCULT DVT

- 349 injured patients: screening venography*
- None receiving prophylaxis
- Proximal DVT rate: 18%
- PE rate: 2% (43% mortality!!)

*Geerts et al, NEJM 1994
Incidence of Occult PE after Trauma

- 90 consecutive patients; ISS > 9
- Asymptomatic; no DVT
- Chest CT: between 3-7 days
- 22 had clot on CT; 4 were major!
- 30% were receiving prophylaxis

Schultz et al J Trauma 2004
The Goddess of Ultrasound
Detection: DVT

- Silent DVT: **10-18%** of high-risk patients
- Surveillance Scanning: Cost-effective in trauma patients: 14 days*
- **30%** of DVT: upper extremity (missed by lower extremity venography)
- Supplement to **inadequate** prophylaxis

* Brasel, J Trauma 1997
Detection of PE

• CT angiography: most commonly used
• Low sensitivity: 50% for central PE *
  28% for peripheral PE
• Multi-slice CT+ neg. D-dimer + neg. duplex: highest sensitivity**
• 1-2% of trauma patients: FATAL PE

*Velmahos J Trauma, 2004; **Perrier NEJM 2005
Initial Study: Knudson et al

- Study #1: 113 patients at Stanford
- Serial scanned: duplex ultrasound
- All patients received prophylaxis:
  - Overall VTE rate: 10%
  - PE rate: 6%!—no PE deaths
  - LDH - same as SCD: effective?
Knudson: Study #1 Results
J Trauma, 1992

Diagram showing bar graphs for age, Days Imm, # RBCs, and PTT sec. with categories for no VTE and VTE.
Knudson: Study #2 J Trauma, 1994

- 251 randomized patients: serial CFD
- LDH vs. SCD vs. Controls
- 6%: DVT; 2 PE: 50% mortality
- SCD only effective in TBI patients
- LDH: no better than nothing
Low Molecular Weight Heparin

- Short heparin chains
- High affinity for antithrombin
- More predictable anticoagulant activity
  - longer 1/2 life
  - bioavailability
  - less bleeding
LMWH in Trauma Patients

- Canadian study: LDUH vs LMWH
  - Venography DVT rate - 15% vs 6%
    - Geerts, NEJW, 1996
- US study: Mechanical vs LMWH
  - Duplex DVT rate - 2.5% vs 0.8%
    - Knudson, J Trauma 1996
Prophylactic Vena Cava Filters?

- Problems:
  - Recurrent PE: 3%
  - No protection against DVT
  - 10%: caval thrombosis
  - permanence: leg edema
  - migration/IVC perforation
  - timing: 6% PE within 24 hours
Retrievable Filters: “NOT”

- May be retrieved within 5 days
- May be left in place: 30 days?
- Solution for high risk patients?
- Leads to 3-fold increase use
- AAST study: >400 patients
- Only 22% were retrieved!
- $100,000/ PE prevented

Antevil J Trauma 2006
Karmy-Jones J Trauma 2007
THROMBOEMBOLISM AFTER TRAUMA

AN ANALYSIS OF 1602 EPISODES FROM THE ACS NATIONAL TRAUMA DATA BANK

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The University of California, San Francisco
NATIONAL TRAUMA DATA BANK

• Largest trauma database available
• Sponsored by the ACS/COT
• Data: 2 million patients
• De-identified data for research

SOURCE: CLINICAL BENCHMARKING
VTE RISK FACTOR ANALYSIS

Hypotheses:

- *Clinical* incidence of VTE - relatively low
- Patients who would benefit from VTE *prophylaxis* could be clearly identified
METHODS

• **Data source:** NTDB (1994-2001)
• **Data analysis:**
  - Demographics
  - Nature/severity of injuries
  - Complications/outcomes
• **Survey:** participating trauma centers
  - VTE risk factors/protocols
RESULTS

- 450,375 patients included
- 84% blunt injuries
- 31% ISS>10
- 998 pts: DVT (0.36%)
- 522 pts: PE (0.13%)
- 82 pts: both DVT/PE
- PE mortality: 18.7%
### RISK FACTOR ANALYSIS

<table>
<thead>
<tr>
<th>Risk Factor *</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shock on admission (BP &lt; 90 mHg)</td>
<td>1.95</td>
</tr>
<tr>
<td>Age ≥ 40 yrs.</td>
<td>2.29</td>
</tr>
<tr>
<td>Head injury (AIS ≥ 3)</td>
<td>2.59</td>
</tr>
<tr>
<td>Pelvic fracture</td>
<td>2.93</td>
</tr>
<tr>
<td>Lower extremity fracture</td>
<td>3.16</td>
</tr>
<tr>
<td>Spinal cord injury with paralysis</td>
<td>3.39</td>
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</table>


p < .0001 for all factors
RISK FACTOR ANALYSIS

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major surgical procedure</td>
<td>4.32</td>
</tr>
<tr>
<td>Venous injury</td>
<td>7.93</td>
</tr>
<tr>
<td>Ventilator days &gt; 3</td>
<td>10.62</td>
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</tbody>
</table>

p < .0001 for all factors
## MULTIVARIATE ANALYSIS

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head injury (AIS $\geq 3$)</td>
<td>1.24</td>
</tr>
<tr>
<td>Major operative procedure</td>
<td>1.53</td>
</tr>
<tr>
<td>Lower extremity fracture (AIS $\geq 3$)</td>
<td>1.92</td>
</tr>
<tr>
<td>Age $\geq 40$ years</td>
<td>2.01</td>
</tr>
<tr>
<td>Venous injury</td>
<td>3.56</td>
</tr>
<tr>
<td>Ventilator days $&gt; 3$</td>
<td>8.08</td>
</tr>
</tbody>
</table>

$p \leq 0.0125$ for all factors
VENA CAVA FILTERS

- Procedure code: “IVC plication”
- 3,883 patients
- 86%: prophylaxis (no VTE)
- PE rate in filter group: 4.7%
- 410 patients: no risk factors
- Permanent IVC filters
SURVEY RESULTS

• Majority: identified risk factors for VTE
• 50%: VTE protocol in place
• Preferred prophylaxis: LMWH
• 16%: VCF-heparin contraindicated
CONCLUSIONS

• Clinically significant VTE rates: low
• 90% VTE pts. have at least 1 risk factor
• VTE risk- varies with each factor
• Role of IVC filters: re-examined
STUDY LIMITATIONS

- Level II recommendations
- **Quality** of data: variable
- **Type II error**: spinal cord injuries
- Risk factors: missed 10% pts with VTE
- Limited data: pre-existing risk factors
- Unable to link prophylaxis with VTE
Spinal cord injuries

- Highest risk trauma patients
- DVT rates: 80%
- PE rates: 5%
- PE-most common cause of death
PROPOSED ALGORITHM

Injured Patient

High Risk Factor
(OR for VTE = 2-3)
- Age ≥ 40
- Pelvic fx
- Lower extremity fx
- Shock
- Spinal cord injury
- Head trauma (AIS ≥ 3)

Contraindication for heparin?
- No
- Yes
  - LMWH*
  - Mechanical compression

Contraindication for heparin?
- No
- Yes
  - LMWH* and mechanical compression
  - Mechanical compression and serial CFD OR temporary IVC filter

VERY High Risk Factor
(OR for VTE = 4-10)
- Major operative procedure
- Venous injury
- Ventilator days > 3
- 2 or more high risk factors

Contraindication for heparin?
- No
- Yes
  - LMWH* and mechanical compression
  - Mechanical compression and serial CFD OR temporary IVC filter

*Prophylactic dose
# DVT Prophylaxis: Patient Charges - SFGH

<table>
<thead>
<tr>
<th>Service Description</th>
<th>Average 2 Week Charge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequential Compression Devices</td>
<td>$679</td>
</tr>
<tr>
<td>- stockings, sleeves, pump</td>
<td></td>
</tr>
<tr>
<td>LMWH</td>
<td>$3,220</td>
</tr>
<tr>
<td>- 30mg/twice daily</td>
<td></td>
</tr>
<tr>
<td>IVC Tulip (insertion/removal)</td>
<td>$10,400*</td>
</tr>
<tr>
<td>- filter and procedure charges</td>
<td></td>
</tr>
<tr>
<td>Serial CFD Scanning</td>
<td>$1,700*</td>
</tr>
<tr>
<td>- scan/tech charges</td>
<td></td>
</tr>
</tbody>
</table>

*Does not include professional fees
Practice Patterns VTE Prophylaxis in Trauma

- 315 patients: 11% VTE
- Early prophylaxis: 4% risk
- Prophylaxis after 4 days: 3 times greater!
Fondaparinux

- Synthetic pentasaccharide; non-heparin
- Selective AT binding: neutralizes Xa
- 300 times innate AT III activity
FONDAPARINUX

- More effective than enoxaparin: ortho
- Less bleeding/lower mortality: acute MI
- Once daily dosing
- No heparin; NO HIT

Turpie NEJM 2001; Yusuf NEJM 2006
Fondaparinux for the Prevention of Venous Thromboembolism in High-Risk Trauma Patients

J.P. Lu, MD

U. Of California, San Francisco
Study Objectives

• To evaluate the **efficacy** and **safety** of fondaparinux for DVT prophylaxis in trauma patients

• To implement a VTE prevention protocol based on **stratified risk factors**

• To measure Fondaparinux **anti Xa activity** in trauma patients
Hypotheses

• VTE rate would be less than 5% in high-risk trauma patients with Fondaparinux
• Fondaparinux: no increased bleeding risk
• Anti-Xa activity would be therapeutic
Methods

• Subjects: consecutive admissions-6 months

• **Inclusion criteria:**
  – Age >=18
  – Risk factor for VTE
  – Anticipated hospital stay >= 5 days

• **Exclusion criteria:**
  – Prisoners
  – Pregnant women
Risk assessment

INJURED PATIENT

High Risk Factors
(Odds ratio for VTE = 2–3)

- Age ≥ 40
- Pelvic fx
- Lower extremity fx
- Shock
- Spinal cord injury
- Head Injury (Ais ≥ 3)

Does the patient have contraindication for anticoagulation?

Yes
- SCDs
- Serial ultrasound

No
- FND*
- Serial ultrasound
- Anti Xa

* Fondaparinux 2.5 mg sq

Very High Risk Factors
(Odds ratio for VTE = 4–10)

- Major operative procedure
- Venous injury
- Ventilator days > 3
- 2 or more high risk factors

Does the patient have contraindication for anticoagulation?

No
- FND*
- SCDs
- Serial ultrasound
- Anti Xa

Yes
- SCDs
- Serial ultrasound
**AND/OR**
- Temporary IVC filter

* FND* = Fondaparinux
Methods

• Study period: 1-21 days
• Ultrasound surveillance on admission and then weekly
• Fondaparinux for DVT prophylaxis if patient had no contraindication; goal: <36hr
• **Anti Xa** activity measured at third or fourth dose
Results: demographics

- Patients who received fondaparinux, n = 81

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<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>43.1 (+/- 19.3)</td>
</tr>
<tr>
<td>Male sex</td>
<td>60 (74%)</td>
</tr>
<tr>
<td>Blunt Injury</td>
<td>51 (63%)</td>
</tr>
<tr>
<td>Mean ISS</td>
<td>18 (+/- 10.1)</td>
</tr>
</tbody>
</table>
Results: incidence of DVT

- With fondaparinux: 2.5%
- Without fondaparinux: 33.3%

Sample sizes:
- With fondaparinux: n = 81
- Without fondaparinux: n = 6
Results: adverse events

- 13 (16%) had decrease in hematocrit
- No transfusions related to the drug
- No other major AEs identified
Results: anti Xa activity

- Trough: 0.05 mg/L
- Peak: 0.3 mg/L
Summary

• Fondaparinux: safe and effective in trauma
• VTE protocol prospectively applied: successfully identified patients at risk
• Further multi-center studies are warranted
Factor VIIa: A New Threat?

- Empiric administration to bleeding patients
- Produces hypercoagulable state early
- Late risk of thromboembolism???
- Early data: small but not significant risk
Protein C: The Unifying Theory

- Trauma patients with shock
- **Hypocoagulable** state
- Protein C gets activated: depleted
- Later become **hypercoagulable**
- **Low protein C**: develop VTE

- *Brohi/Cohen: Annals of Surgery 2006*
DVT/PE Rate In Combat Injuries?

- Combination of very severe injuries
- Burns/Blasts/Fractures
- Prolonged immobilization
- Prolonged air travel > 5,000 miles
Civilian vs Combat Burn Patients

- Retrospective review: 1107 patients
- Evacuated soldiers: younger, higher ISS
- Higher incidence of inhalation injuries
- Clinical incidence of VTE: 0.99% overall
- 1.31% in soldiers vs. 0.83% in civilians

Chang et al 2007
Military experience: rFVII and DVT

- 615 patients: JTTR
- Retrospective review-clinical incidence
- Overall DVT rate: 7.5%; PE rate 3.8%
- Massive Transfusions: 13%
- Massive transfusions and rFVII: 18%
- Prospective study needed
- Have Sonosite will scan!!!
A Great Privilege!