VTE Prevention: From Filters to Fondaparinux

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No Current Disclosures

• Prior Support: Glaxo; Kendall; Rhone-Poulenc

CASE PRESENTATION

• 21 year old chef stabbed in the Mission
• Hypotensive on arrival with evisceration
• Massive transfusion; thoracotomy
• “tacos in the field”: stomach repair x 2
• Splenectomy; distal pancreatectomy
• Extubated after just 24 hours
• 3 days later: fever, tachycardia
Case Presentation Continued

• Full-dose anticoagulation with heparin
• Lower GI bleed with drop in Hematocrit
• Transfused; **IVC Filter placed**
• Prophylatic doses of enoxaparin
• Eventually transitioned to Coumadin

Historical Perspectives

“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
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

THROMBOEMBOLISM AFTER TRAUMA

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

Annals of Surgery 2004

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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>


RISK FACTOR ANALYSIS (CONT')

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator days &gt; 3</td>
<td>10.62</td>
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<tr>
<td>Venous injury</td>
<td>7.93</td>
</tr>
<tr>
<td>Major surgical procedure</td>
<td>4.32</td>
</tr>
</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>Ventilator days &gt; 3</td>
<td>8.08</td>
</tr>
<tr>
<td>Venous injury</td>
<td>3.56</td>
</tr>
<tr>
<td>Major operative procedure</td>
<td>1.53</td>
</tr>
<tr>
<td>Lower extremity fracture (AIS ≥ 3)</td>
<td>1.92</td>
</tr>
<tr>
<td>Age ≥ 40 years</td>
<td>2.01</td>
</tr>
<tr>
<td>Venous injury</td>
<td>3.56</td>
</tr>
<tr>
<td>Head injury (AIS ≥ 3)</td>
<td>1.24</td>
</tr>
</tbody>
</table>

p ≤ 0.0125 for all factors
**PROPOSED ALGORITHM**

**Injured Patient**

**High Risk Factor**
- Age ≥ 40
- Pelvic fx
- Lower extremity fx
- Shock
- Spinal cord injury
- Head trauma (AIS ≥ 3)

**Contraindication for heparin?**
- No
- Yes

**LMWH**
- Yes
- Mechanical compression

**Very High Risk Factor**
- 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

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**“APPEARANCES ARE DECEPTIVE”**


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**Historical Perspectives**
- **1850**: Rudolph Virchow described PE
- Recognized origin in femoral/pelvic veins
- **1910**: Trendelberg ligated IVC for PE
- **1948**: Only 48 cases of IVC ligation

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**IVC Plication**
- IVC Ligation: post-op edema/ulceration
- IVC Ligation: Sudden hypotension!
- IVC Plication: absorbable sutures: unpredictable
- **1964**: IVC Clip
IVC Filters: Indications

- Recurrent VTE despite adequate anticoagulation
- Documented VTE but with contraindications to anticoagulation
- Complications while on anticoagulation

“Filter Fever”

From Filter Fever to Filter Failure

- Technical
- Timing
- Truth
- Trievable (as in Re)
- Tale

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
TIMING

• PE-occurs within 24 hours of injury: 6%*
• PE-seen on CT on day 1: 38%**
• Early PE: highest in patients with fractures
• For filter to be effective: placement in ED?

*Owens 1997
**Scalea 2007

TRUTH

Independent Risk Factors | Odds Ratios
-------------------------|-----------------|
Head Injury (AIS≥3)      | 1.24            |
Major Operation          | 1.53            |
Lower Extremity Fx (AIS≥3)| 1.92            |
Age > 40 years           | 2.01            |
Venous Injury            | 3.56            |
Ventilator Days >3       | 8.08            |

TRUTH: PART II

- 3,883/450,375: IVC FILTERS
- 86%: PROPHYLACTICALLY
- 410 PATIENTS: NO RISK FACTOR!

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

FICTION FEVER (AS IN “PULP”)

Hospital-Specific Risk Factors for Filter Fever

- 263 Northern California Hospitals
- Frequency of VCF for VTE varied widely
- Risk of getting a filter for acute VTE:
  - Admission to Rural Hospital
  - Admission to small hospital
  - Admission to private hospital
  - Not admitted to Kaiser

JAMA 2013
Fondaparinux For The Prevention Of Venous Thromboembolism In High-risk Trauma Patients

J.P. Lu, MD and M. Margaret Knudson
U. Of California, San Francisco

Fondaparinux
• Synthetic, non-heparin polysaccharide
• Long half life: once-daily dosing
• Excreted unchanged by kidney
• Effective in orthopedics and general surgery
• Previously untested in trauma

Mechanism Of Action
• Binds to antithromin III, which inactivates factor Xa, preventing thrombin formation

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** would NOT cause bleeding
- Anti-Xa activity would be therapeutic

### Methods

- **Subjects:** consecutive trauma admissions
- **Inclusion criteria:**
  - Age $\geq 18$
  - Risk factor for VTE
  - Anticipated hospital stay $> 5$ days
- **Exclusion criteria:**
  - Prisoners
  - Pregnant women

### Proposed Algorithm

**Injured Patient**

- **High Risk Factor** (OR for VTE $= 2\text{-}3$)
  - Age $\geq 40$
  - Pelvic fx
  - Lower extremity fx
  - Shock
  - Spinal cord injury
  - Head trauma (AIS $\geq 3$)

- **Contraindication for heparin?**
  - No
  - Yes

  - **FND: 2.5mg**
  - **Mechanical compression**

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

- **Contraindication for heparin?**
  - No
  - Yes

  - **FND and mechanical compression**
  - **Mechanical compression and serial CFD OR temporary IVC filter**

### Protocol

- **Enrollment after consent**
- **Ultrasound on admission and Q 5-7 days**
- **Included both upper and lower extremities**
- **Fondaparinux within 36 hours**
Results: Enrollment

Enrolled Patient, $n = 106$

- fondaparinux: $n=89$
  - excluded: $n=12$
  - excluded after late crossover: $n=2$

- No fondaparinux: $n=17$

Results: Risk Factors

- Major Operation
- Age $> 40$
- LE Fx
- SBP $< 90$
- Mech
- Vent $> 72$ hr
- Pelvic Fx
- Venous injury

Results: Incidence Of DVT

- fondaparinux: $2/81$, $2.5\%$
- No fondaparinux: $2/6$, $33.3\%$
Results

- 2 DVTs in Fondaparinux: 1 with PIC line; 1 on initial scan prior to receiving drug*
- **No bleeding** associated with Fondaparinux
- **No thrombocytopenia**
- No other major AEs identified

*intent to treat

Results: Anti Xa Activity

<table>
<thead>
<tr>
<th>mg/L</th>
<th>Trough</th>
<th>Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td></td>
<td>0.3</td>
</tr>
</tbody>
</table>

Summary

- Fondaparinux has several advantages:
  - No risk of HIT
  - Once daily dosing: **improves compliance**
  - Cost effective
- No major bleeding episodes or AEs
Conclusions

- Fondaparinux: safe and effective in trauma
- **DVT rate:** < 2% in high-risk patients
- Algorithm: identified all high-risk patients
- Combination of algorithm and Fondaparinux: Promising new approach to DVT prophylaxis

Practice Patterns VTE Prophylaxis in Trauma

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

Historical Perspective: Pulmonary Emboli

- Recognized post-injury complication: 1934*
- Mortality rates: **25-50%**
- Clinical presentation: acute hypoxia, collapse
- Diagnostic study: **autopsy**

*McCartney, Am J Pathology*
Current Perspective: PE

- “Potentially preventable” complication
- Clinical Presentation: unexplained drop PaO₂
- Often incidental finding: multidetector CT scan
- Quality indicator: CMS, JACHO, AHRQ

Purpose

- To describe the current incidence of pulmonary embolism following trauma in the United States
- To determine the PE-attributable mortality

Major Hypotheses

1. Risk factors for PE-different from DVT
2. PE-incidence rates are increasing
3. PE-attributable mortality is decreasing

Methods

- ACS/NTDB
  - Adult patients: Level I/II centers*
  - Current version: 2007-2009
  - Historical comparison: 1994-2001 (version 1)
  - Comparison: centers contributing to both
  - Hierarchical logistic regression models: risk factors, mortality
* (centers reporting at least one complication)
Results: Current NTDB Cohort

- 888,652 Patients; 326 Trauma Centers
- Overall mortality: 1.8%
- 9,398 episodes: DVT (1.06%)
- 3,738 episodes: PE (0.42%)
- Only 20% with PE had DVT reported

Results: IVC Filters

- 16,809 patients: 1.9% of total population
- 13,201: Prophylactic
- Center clustering: 0%-10.6%

Risk Factor Analysis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>DVT (9,398); OR (95% CI)</th>
<th>PE (3,738); OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe TBI</td>
<td>1.34 (1.20-1.48)*</td>
<td>0.87 (0.73-1.06)</td>
</tr>
<tr>
<td>Ventilator Days &gt;3</td>
<td>5.31 (5.05-5.60)*</td>
<td>3.81 (3.48-4.16)</td>
</tr>
<tr>
<td>Severe Chest Injury (AIS&gt;3)</td>
<td>1.07 (1.01-1.12)</td>
<td>1.42 (1.30-1.55)*</td>
</tr>
<tr>
<td>Lower Ext. Fracture (AIS&gt;3)</td>
<td>1.53 (1.45-1.62)</td>
<td>1.81 (1.67-1.97)</td>
</tr>
<tr>
<td>Pelvic Fracture</td>
<td>1.32 (1.24-1.41)</td>
<td>1.19 (1.08-1.32)</td>
</tr>
<tr>
<td>Spine Injury (AIS&gt;4)</td>
<td>1.58 (1.42-1.75)</td>
<td>1.91 (1.61-2.27)</td>
</tr>
<tr>
<td>Shock (SBP&lt;90)</td>
<td>1.23 (1.14-1.34)</td>
<td>1.19 (1.04-1.36)</td>
</tr>
</tbody>
</table>

Changes over Time: PE

<table>
<thead>
<tr>
<th></th>
<th>Historical Number (%)</th>
<th>Adjusted OR (95% CI)</th>
<th>Current Number (%)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE Rate</td>
<td>499 (0.21%)</td>
<td></td>
<td>890 (0.49%)</td>
<td></td>
</tr>
<tr>
<td>Mortality-PE</td>
<td>73 (15%)</td>
<td>3.03 (2.02-5.46)</td>
<td>111 (11%)</td>
<td>2.42 (1.91-3.06)</td>
</tr>
</tbody>
</table>
Discussion: Potential Explanation

- 1. True increased incidence of PE
- 2. Better reporting in NTDB/NTDS
- 3. “Sicker” patients in current cohort
- 4. Failure of VTE prophylactic measures
- 5. Improved methods of detection

Uncoupling DVT and PE

Severely Injured Patient
- Shock
- Coagulopathy

Hypersusceptible State

TBI
Fractures
Venous Injury
Chest Injury
Inflammation

Protein C Depletion?

DVT

PE rates versus Prophylactic IVC filters

<table>
<thead>
<tr>
<th>PE rates</th>
<th>Prophylactic IVC Filters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Historical</td>
<td>Current</td>
</tr>
<tr>
<td>0.00%</td>
<td>0.00%</td>
</tr>
<tr>
<td>0.10%</td>
<td>0.20%</td>
</tr>
</tbody>
</table>

Conclusions

- PE: increasingly recognized post injury
- PE: decreased attributable mortality
- PE: may develop de novo
- PE: chest trauma/inflammation
- PE: may not be prevented by filters
Knudson’s Trauma Triad
- Paralysis
- Immobilization
- Venous trauma
- Stasis
- Severe injuries
- Endothelial damage
- Hypercoagulability

Knudson’s Trauma Square
- Venous trauma
- Fractures
- Chest trauma
- Endothelial damage
- Inflammation
- Stasis
- Hypercoagulability

MILITARY EXPERIENCE WITH VTE
- High amputation rate: “dismount” injuries
- Massive transfusions and shock
- Prolonger Air-Evac
- Screening: **14.5% DVT RATE**
- Screening: **4.42% PE RATE**
- Thrombosis post-blast?

POC Coagulation Monitoring
- Thrombelastograph (Haemoscope Corp.)
- Sonoclot (Sienco Inc.)
**TEG Monitoring of Enoxaparin**

- Standard prophylactic doses are inadequate in some patients: anti-Xa levels
- TEG-based dosing decreased DVT
- Prospective multicenter study

  - Malowski J Trauma 2010; Van J Trauma 2009

**VTE PROPHYLAXIS IN TBI**

- Progression of the injury vs. PE
- **DEEP I Study**: enoxaparin safe at 72 hours*
- **SFGH/TEG Study**: Normal at 24 hours*
- Severe TBI: hypercoagulable

  Phelan et al J Trauma 2012  
  Phelan: J Neurotrauma 2012  
  Cohen: unpublished

**THE ORIGINAL MISSION HOSPITAL**

**SFGH: AS REAL AS IT GETS!**
BADASS GRL: PE Prevention Possible. Think outside