What About The Nuts And Bolts – Heparin, PTT and Fibrinogen Monitoring, And How Do You Know When You Are Done

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Disclosures

• Current
  – Medtronic – Consultant/ Speaker
  – Bard – Data Safety Committee
  – Cook – Consultant
  – Volcano – Consultant
  – Boston Scientific – Consultant/ Speaker
• Concluded
  – Synvacor – Director – Core Lower Extremity Wound Lab
  – GSK – Drug support only

HEPARIN USE

Hemodynamically stable patients with acute symptomatic PE
UFH 80 U/kg Bolus IV, UFH continuous infusion of 18 U/kg/min IV (max 1800 U/h)
Contrast-Enhanced Chest CT:
Filling defect in at least one main or proximal lower lobe pulmonary artery
Baseline ECHO: RV/LV ratio > 1
Secondary endpoints: Mortality, recurrent PE, major & minor bleeding at 90 days

ULTIMA Trial

Primary endpoints:
Reduction in RV/LV ratio from baseline to 24h
Secondary endpoints: Mortality, recurrent PE, major & minor bleeding at 90 days

Seattle II

Standard Anticoagulation for PE
UFH goal PTT 40-60 sec during procedure
Catheter Placement and Treatment Based on Extent of Disease
Unilateral: 1 catheter infusing t-PA 1 mg/hour for 24 hours
Bilateral: 2 catheters infusing t-PA 1 mg/hour/catheter for 12 hours
Baseline Right Heart Catheter Measurements
Including pulmonary artery systolic pressure
Ultrasound-Facilitated, Low-Dose, Catheter-Directed Fibrinolysis

PEITHO

Am Heart J 2012;163:33-38.e1
CAVENT TRIAL

• “UFH with aPTT at 1.2 – 1.7 times higher than the upper normal limit”

ATTRACT

• Heparin during PMT – 6-12 U/kg/hr or LMWH 1m/kg Q 12.

Heparin Monitoring

• PTT Use
  – Therapeutic Target – 1.5 to 2.5 baseline
  • Based on a rabbit model of thrombosis
  • Early clinical observation – decreased recurrent thrombosis when therapeutic levels are achieved rapidly and are adequately maintained
  • Clinical relevance of this therapeutic range – UNCERTAIN
    (not been confirmed by randomized trials)
  • Established a therapeutic range for the aPTT (1.5 to 2.5) =
    – Heparin level of 0.3 to 0.7 units measured by an anti-Xa assay

When to use Anti-Xa?

• Heparin resistance
  – Patients require unusually high doses of heparin to achieve a therapeutic state
  – AT deficiency
  – High levels of factor VIII and/or fibrinogen
• Obese
• Pregnancy
• Critically ill
• Baseline prolonged aPTT (APLA)

Discordant pattern = Poor clinical outcomes!!

• Patients with consistently high aPTT values relative to anti-Xa values who were not on warfarin
  – Had increased 30 day mortality.
• Patients with a relatively high aPTT to anti-Xa value on at least 2 consecutive occasions
  – Had increased 21 day major bleeding rates

Any value for steady state anticoagulation?

• EINSTEIN PE investigators and patients
• Anticoag – Enoxaparin/ VKA Vs Rivaroxaban
• 3 weeks – clot resolution on CTA/ Q Scan
Clot Burden Reduction

- Aggressive monitoring of INRs leads to good outcomes
- Steady state AC may be a good thing

**Low dose antithrombotic therapy + Lysis**

- Low dose UFH as partner during fibrinolysis in prolonged lytic infusions
  - Based on Coronary intervention data.
  - Usual dose 500-800 U/hr during lysis

ACT Measurements

Range of 350 to 375s for PCI

General preference - 250-300s

Fibrinogen

- rtPA’s – has incomplete fibrin specificity
  - Extends to circulating fibrinogen
  - Fibrinogen molecules are cleaved into fibrinogen degradation products including fragments X, Y, D, and E.
  - Some of these fragments have anticoagulant properties

Fibrinogen Level and Bleeding Risk During Catheter-Directed Thrombolysis Using Tissue Plasminogen Activator

- Forty-two patients (17 arterial and 25 venous)
- 0 to 10 mg bolus of tPA followed by infusion at 0.5 to 2 mg/hour until angiography showed resolution of the thrombus + 500U/Heparin
- Infusion rate – decreased by half if the fibrinogen level fell below 1.5 g/L
- stopped if the fibrinogen level fell below 1 g/L
- Major bleed = ICH/ transfusion/ surgical re-intervention
Univariate analysis identified total tPA amount (P < .01) and duration of tPA (P < .03) as predictors of major and minor bleeding.

<table>
<thead>
<tr>
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<th>Low Fibrinogen</th>
<th>High Fibrinogen</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Major mortality</td>
<td>1 (6.3%)</td>
<td>0 (0.7%)</td>
<td>.139</td>
</tr>
<tr>
<td>Minor mortality</td>
<td>2 (12.5%)</td>
<td>3 (18.8%)</td>
<td>.293</td>
</tr>
<tr>
<td>Technical failure</td>
<td>1 (6.3%)</td>
<td>0 (0.7%)</td>
<td>.465</td>
</tr>
<tr>
<td>Clinical failure</td>
<td>1 (6.3%)</td>
<td>0 (0.7%)</td>
<td>.381</td>
</tr>
<tr>
<td>Length of stay</td>
<td>6.8 ± 3.4</td>
<td>10.0 ± 12.1</td>
<td>.123</td>
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<tr>
<td>Secondary procedure</td>
<td>3 (18.8%)</td>
<td>3 (11.5%)</td>
<td>.496</td>
</tr>
<tr>
<td>Endovascular</td>
<td>3 (18.8%)</td>
<td>3 (11.5%)</td>
<td>.496</td>
</tr>
<tr>
<td>Surgical</td>
<td>2 (12.5%)</td>
<td>7 (26.9%)</td>
<td>.496</td>
</tr>
</tbody>
</table>

When to stop?

- Clinical end points PE
  - Hemodynamics
  - PA catheter pressures
  - PA gram?
  - Echo?

ENOUGH IS ENOUGH…. WHEN THE PATIENT STARTS FEELING BETTER....

Thank you