Ultrasound-Facilitated Delivery of Lytics

S. Jay Mathews, MD, MS, FACC

Interventional Cardiologist/Endovascular Specialist
Bradenton Cardiology Center
Clinical Associate Professor, LECOM
Bradenton, FL
Disclosures

Speaker’s Bureau:
• Astra Zeneca
• Maquet
• Spectranetics

Grant/Research Support
• Astra Zeneca
• Terumo
• Cordis
• Medtronic
• Bard
• Veryan Medical
• Spectranetics

Medical/Scientific Boards:
• Abbott Vascular
Clinical Profile

• 56 Year Old Woman presents with severe dyspnea for 3 days
  • Obese
  • Sedentary
  • Mild LE Swelling Bilaterally
  • Troponin 0.26
  • pBNP Elevated
  • Hypoxemic with O2Sat 90% on 100% NRB
  • CTA with Bilateral PE and RV Strain
EkoSonic System (Ekos)

- 5.4 Fr Catheters
- 106 and 135 cm Working Length
- Multiple Treatment Lengths
  - 6, 12, 18, 24, 40, and 50 cm
Ultrasound-Facilitated Mechanism

**Fibrin Separation**
Ultrasound separates fibrin without fragmentation of emboli


**Active Drug Delivery**
Drug is actively driven into clot by "Acoustic Streaming"
Acoustic Pulse Thrombolysis (APT)

• Ultrasonic energy thins fibrin strands, loosens them, and exposes plasminogen receptor sites
• This improves thrombus permeability increasing lytic penetration
• Ultrasound forces the lytic to stay within the clot with acoustic pressure

Biological activity thus may continue within the thrombus even without detectable plasma levels of rtPA

1) rtPA binds fibrin in thrombus
2) plasminogen gets converted to plasmin
3) local fibrinolysis initiated into FDPs

Ultrasound-Facilitated Mechanism

- Registry of 53 Patients with Multiple Lytics
- Acoustic Pulse Thrombolysis achieved clearance with lower lytic dose and infusion time than CDT

<table>
<thead>
<tr>
<th></th>
<th>Urokinase</th>
<th>Alteplase (t-PA)</th>
<th>Reteplase (r-PA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EKOS*¹(n=14)</td>
<td>CDT²(n=38)</td>
<td>EKOS*¹(n=9)</td>
</tr>
<tr>
<td><strong>Median Drug Dose</strong></td>
<td>2.02 MU</td>
<td>4.36 MU</td>
<td>14.0 mg</td>
</tr>
<tr>
<td><strong>Median Infusion Time</strong></td>
<td>19.3 hr.</td>
<td>40.6 hr.</td>
<td>18.0 hr.</td>
</tr>
</tbody>
</table>

Ultrasound-Facilitated Mechanism

- 178 patients with acute (14 days) or chronic (>14 days) DVT
- Measured angiographic clearance and clinical improvement with acoustic pulse thrombolysis compared with pharmacomechanical therapy (AngioJet or Trellis)

<table>
<thead>
<tr>
<th></th>
<th>PMT only AngioJet</th>
<th>PMT only Trellis</th>
<th>APT only EKOS®</th>
</tr>
</thead>
<tbody>
<tr>
<td>100% angiographic clearance</td>
<td>39%</td>
<td>0%</td>
<td>64%</td>
</tr>
<tr>
<td>Decrease in pain and/or swelling</td>
<td>28%</td>
<td>33%</td>
<td>64%</td>
</tr>
</tbody>
</table>

**Ultrasound-Facilitated Mechanism**

- Prospective study of 87 consecutive iliofemoral DVT patients treated with EKOS and stenting of underlying venous stenosis
- Fixed dose regimen of EKOS as primary therapy with 20 mg tPA over 15 hours
- Follow up at 3, 6, and 12 months measuring primary treatment success (Villalta PTS scale and CEAP classification)
- 1 major bleeding (1%), 6 minor bleedings (7%)

<table>
<thead>
<tr>
<th></th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>No PTS</td>
<td>88%</td>
<td>92%</td>
<td>94%</td>
</tr>
<tr>
<td>No visible signs of venous disease</td>
<td>51%</td>
<td>53%</td>
<td>61%</td>
</tr>
</tbody>
</table>

Engelberger et al. Fixed Low-dose ultrasound-assisted catheter-directed thrombolysis followed by routine stenting or residual stenosis for acute ilio-femoral deep-vein thrombosis; *Thrombosis and Haemostasis* 111.6/2014.
Rationale for Lytics in PE

- Reduce Thrombus Burden (not achievable by AC alone)
- Reverse RV afterload/failure toward prevention of hemodynamic collapse
  - In a prospective study of 2454 consecutive PE patients there was a 57% increased risk of mortality with persistent RV dysfunction
- Improve pulmonary reperfusion/capillary blood flow/gas exchange
- Restore systemic arterial perfusion pressure
- Decrease the risk of developing chronic pulmonary hypertension

Mortality rate at 3 months

- 21% with hypokinesis
- 15% with no hypokinesis

Nycamp Study

• Single-center retrospective study to evaluate safety and efficacy of EKOS therapy
• n=45
• Comparison to separate control group (n=45) of intermediate to high-risk PE patients treated with systemic heparin or anticoagulation alone
• Average LoS: EKOS treated = **3.2 days** versus AC = **6.7 days**

ULTIMA Trial- Prospective RCT

- 59 Patients- Randomized to rtPA or UFH
- Infusion Protocol
  - rtPA 1mg/h; saline coolant 35ml/h
  - Patients monitored in the intermediate or ICU
  - After five hours, rtPA reduced to 0.5 mg/h
  - At 15(+/−) hours, rtPA infusion, saline coolant and ultrasound discontinued

ULTIMA Trial

• Systolic RV Dysfunction Improved

ULTIMA Trial

- No Increased Risk of Bleeding Over UFH

<table>
<thead>
<tr>
<th>Clinical outcomes at 90 days</th>
<th>EKOS with tPA + Heparin N= 30</th>
<th>Heparin N= 29</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>1*</td>
<td>0.49</td>
</tr>
<tr>
<td>Recurrent venous thromboembolism</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>3**</td>
<td>1</td>
<td>0.61</td>
</tr>
</tbody>
</table>

SEATTLE II Trial- Prospective Single Arm

Evaluate EKOS for massive and submassive PE (n=150; 22 centers):

- Efficacy – as measured by reduction in RV/LV ratio
- Safety – as measured by major bleeding within 72 hours

Protocol

- If unilateral PE: tPA 1 mg/hr using one device for 24 hours
- If bilateral PE: tPA 1 mg/hr per device (using two simultaneously) for 12 hours

**25% DECREASE IN RV/LV OVER 48 HOURS**

<table>
<thead>
<tr>
<th></th>
<th>Pre-Procedure</th>
<th>48 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV/LV Ratio</td>
<td>1.55</td>
<td>1.13</td>
</tr>
</tbody>
</table>

*P<0.0001*

**RAPIDLY RELIEVED PA OBSTRUCTION**

<table>
<thead>
<tr>
<th></th>
<th>Pre-Procedure</th>
<th>48 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Modified Miller Score</td>
<td>22.5</td>
<td>15.8</td>
</tr>
</tbody>
</table>

*P<0.0001*

SEATTLE II Trial

- Significant Reduction in PH at 48 Hrs
- No Cases of ICH
- Only 2 Cases (1.8%) of rtPA-Related Complications

Back to the Case

- Large Iliocaval DVT
- Bilateral PE
- May Explain the Lower Extremity Swelling
Back to the Case

- Large Iliocaval DVT
- Bilateral PE
- May Explain the Lower Extremity Swelling
- Two Catheters Placed in Bilateral PA- One 50 cm (Left) and One 12 cm (Right)
Back to the Case

- Large Iliocaval DVT
- Bilateral PE
- May Explain the Lower Extremity Swelling
- Two Catheters Placed in Bilateral PA - One 50 cm (Left) and One 12 cm (Right)
Back to the Case

• Post-EKOS
  • Normalization of O2 Sat
  • Patient on RA 94%
  • Clinically Better
  • Residual Thrombus in IVC, But Angiographic Lucency Has Changed
Back to the Case

- Crux Temporary Filter Placed
- 8F Angiojet Zelante Used
- Angiographic Thrombus Resolution
- Filter Removed
- Patient was Later Diagnosed with NSCLC
- Discharged on Therapeutic Coumadin
Ultrasound-Facilitated Delivery of Lytics

S. Jay Mathews, MD, MS, FACC

Interventional Cardiologist/Endovascular Specialist
Bradenton Cardiology Center
Clinical Associate Professor, LECOM
Bradenton, FL