Innovative Endovascular Approach to Pulmonary Embolism by Ultrasound Enhanced Thrombolysis

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Catheter Directed Thrombolysis: The Magic Bullet for Submassive Pulmonary Embolism?
• Catheter-based thrombolysis

  – Local administration of lytic agent
  – Higher local drug concentration results in more rapid and complete thrombolysis
  – Even distribution results in faster treatment of thrombus
• Standard PE therapy

ANTICOAGULATION (AC) – HEPARIN
– AC therapy prevents further clot growth
– Studies\(^1\)\(^-\)\(^3\) found:
  – LMWH as effective as UFH in reducing recurrent PE
  – LMWH carries reduced bleeding risk compared to UFH

STANDARD OF CARE: usually UFH or LMWH, followed by oral warfarin
– However, AC therapy relies on endogenous t-PA to dissolve occluding clot\(^4\)
  – a process that typically occurs over several weeks or months
  – endogenous fibrinolysis may often be incomplete at the end

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Why do we treat these patients at all?
• Rationale for thrombolysis in acute PE

REDUCE THROMBUS BURDEN (not achievable by AC alone)
– Reverse RV afterload / failure toward prevention of haemodynamic collapse
– Improve pulmonary reperfusion/capillary blood flow / gas exchange
– Restore systemic arterial perfusion pressure
– Decrease the risk of developing chronic pulmonary hypertension

• IV thrombolysis with t-PA

100 mg t-PA infused over 2 hours
Indicated for management of acute massive PE in adults:

- For the lysis of acute pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments of the lungs.
- For the lysis of pulmonary emboli accompanied by unstable haemodynamics, e.g., failure to maintain blood pressure without supportive measures.
But the benefit of lysis came at the cost of major bleeds (including ICH)

<table>
<thead>
<tr>
<th></th>
<th>Tenecteplase (n=506)</th>
<th>Placebo (n=499)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All strokes by day 7</td>
<td>12 (2.4%)</td>
<td>1 (0.2%)</td>
<td>0.003</td>
</tr>
<tr>
<td>– Haemorrhagic</td>
<td>10</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>– Ischemic</td>
<td>2</td>
<td>0</td>
<td></td>
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<tr>
<td>Serious adverse events (SAE)</td>
<td>29 (5.7%)</td>
<td>39 (7.8%)</td>
<td>0.19</td>
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</tbody>
</table>

http://clinicaltrialresults.org/Slides/ACC%202013/Konstantinides_PEITHO_ACC%202013.pdf
• Adverse outcomes associated with RVD

Echocardiographic RV/LV ratio $\geq 0.9$ shown to be independent predictive factor of hospital mortality

- Registry of 1,416 patients
- Mortality rate:
  - 1.9% if RV/LV ratio < 0.9
  - 6.6% if RV/LV ratio $\geq 0.9$
Patients with RVD defined as RV/LV >0.9 have a greater chance of adverse events within 30 days.

- Retrospective analysis of 63 patients with chest CT
- Adverse event rate at 30 days:
  - 80.3% if RV/LV ratio > 0.9
  - 51.3% if RV/LV ratio ≤ 0.9
• Review of the clinical evidence for EKOS® for the treatment of PE

- ULTIMA trial
- SEATTLE II trial
- Meta-analysis of historical published data
- Recent single-center studies
• ULTIMA study compared EKOS® to heparin in intermediate risk PE therapy

The first RCT for an advanced catheter-based modality

Primary Objective: Determine whether fixed low-dose catheter-directed ultrasound accelerated thrombolysis is superior to heparin alone in reversal of RV dilatation in submassive / intermediate risk PE

• **EkoSonic® Endovascular System**

**Features**
- 5.4 Fr catheter
- 106 and 135 cm working length
- 6, 12, 18, 24, 30, 40 and 50 cm treatment zones
Fibrin Separation
Non-cavitational ultrasound separates fibrin without fragmentation of emboli

Fibrin without Ultrasound
Fibrin With Ultrasound

Active Drug Delivery
Drug is actively driven into clot by “Acoustic Streaming”

Acoustic streaming drives lytic into clot

EKOS® Acoustic Pulse Thrombolysis™ is a minimally invasive system for dissolving thrombus.

• EkoSonic® Endovascular System
  • Mechanism of action

How ultrasonic energy unlocks the clot

- Ultrasonic energy causes fibrin strands to thin, exposing plasminogen receptor sites and fibrin strands to loosen
- Thrombus permeability and lytic penetration are dramatically increased
- Ultrasound pressure waves force lytic agent deep into the clot and keep it there

• **EkoSonic® Endovascular System**

Placement in the left and right pulmonary arteries for the treatment of bilateral PE
• SEATTLE II examined EKOS® benefit in a clinical trial setting in the US

Patients
Acute Massive and Submassive PE with RV/LV ratio ≥ 0.9
(n = 150; 22 centers)

Objectives
Evaluate ultrasound-facilitated, catheter-directed low-dose fibrinolysis:
• Efficacy – as measured by reduction in RV/LV ratio
• Safety – as measured by major bleeding within 72 hours

- Ultrasound-facilitated fibrinolysis using EKOS®
  - 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

Follow up at 48 +/- 6 hours
- CT measurement of RV/LV ratio
- Echocardiogram to estimate PA systolic pressure

### The SEATTLE II Study

- **Patient characteristics and treatment details**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td><strong>Total enrollment</strong></td>
<td>150*</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Massive / Submassive PE</strong></td>
<td>31 / 119</td>
<td>21% / 79%</td>
</tr>
<tr>
<td><strong>History of previous DVT</strong></td>
<td>30</td>
<td>20%</td>
</tr>
<tr>
<td><strong>History of previous PE</strong></td>
<td>15</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Concomitant use of antiplatelet agents</strong></td>
<td>51</td>
<td>34%</td>
</tr>
<tr>
<td><strong>Unilateral / Bilateral PE</strong></td>
<td>20 / 130</td>
<td>13% / 87%</td>
</tr>
<tr>
<td><strong>Total rtPA dose</strong></td>
<td></td>
<td>23.7 ± 2.9 mg</td>
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* Denotes 1 patient died prior to treatment

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Reduced RV/LV ratio and Modified Miller Score at 48 hours post-EKOS®


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• Reduced pulmonary artery pressure immediately post-procedure


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Single center experience showed CTA evidence of RVD resolution

- Single center retrospective single arm study
- 24 patients with high risk (n=5) or intermediate risk (n=19) PE treated with EKOS®
- Mean rtPA dose was $33.5 \pm 15.5$ mg over 19.7 hours
- No deaths or systemic bleeding complications, including intracranial haemorrhage; 4 access site bleeds requiring transfusion

<table>
<thead>
<tr>
<th></th>
<th>Pre-EKOS®</th>
<th>Post-EKOS®</th>
<th>P value</th>
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<tbody>
<tr>
<td>RV/LV ratio</td>
<td>1.33 ± 0.24</td>
<td>1.00 ± 0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Modified Miller Score</td>
<td>17.8 ± 5.3</td>
<td>8.7 ± 5.1</td>
<td>&lt;0.001</td>
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</tbody>
</table>

• Modified Treatment Protocol

Initial Injection 5 mg rtPA

20 mg rtPA in 1 PA or

10 mg rtPA in each PA

Duration: 2 h
Sub Massive PE
59 years old female patient

Left Iliac vein Thrombosis

RV / LV Ratio: 1,4

Ekos, Venous Aspiration Thrombectomy
Massive PE

87 year old female Patient

DVT: Left Iliac Vein, Femoral Vein
Massive PE
CARDIO – Pulmonary Arrest
EKOS bilateral PA Catheters
RV / LV Ratio: 1,5
Discharged after 9 days
RV / LV Ratio: 0,9
Massive PE: 8 Patients
Submassive PE: 15 Patients
Duration of Symptoms: 2,2 (0 -6) Days

- 23 Patients
- Intention to treat 22
- Resuscitations: 2
- 1 PA Catheter: 12
- 2 PA Catheters 9
- Mortality 1
- Rejected 1
- Ven.Thrombectomy 4
- Major AE (incl.Bleeding) 0
- V Cava Filter 1

Modified Miller Score

RV / LV Ratio pre. - post
50 % Thrombus Resolution in half of all patients yet significant drop in PA pressure.

Sometimes Less is More in high risk patients!

- PA Pressure
  - Before
  - After
Modified Protocol

• Only 2 (8.6%) patients treated in ICU

• 91% treated in Intermediate Care Unit or Recovery Room

• No Bleeding Complications

• No Access Site Complications
CONCLUSION

Ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute PE improves RV function and decreases pulmonary hypertension and angiographic obstruction. By minimizing the risk of intracranial bleed, it represents a potential “game-changer” in the treatment of high-risk PE patients.