Step-By-Step Technical Tips for Pharmaco – Mechanical Intervention for PE

Use to be Called Catheter Directed Thrombolysis

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Conflicts of Interest

- Consultant
  - Abbott Vascular
  - Boston Scientific
  - Medtronic
  - Cook Medical
  - Spectranetics
  - WL Gore
  - CR Bard
  - Primacea
  - Venarum
  - Spectranetics/Philips
  - Venarum
  - Reflow Medical

- Equity
  - Primacea
  - Reflow medical

- Royalties
  - Cook Medical

Benefits of Pharmaco-Thrombolysis

- Small Access
- Traditional size catheters through right heart and pulmonary artery
- More universally available skill sets

When To Utilize Pharmaco-Mechanical Thrombolysis?

- Massive PE that has contraindication to full dose lytic
- Sub-massive Elevated risk?
- Locked Lung?

Don’t Be Frozen by Indecision

- Majority of patients eligible for thrombolysis do not receive it
- Hypotension
- Abnormal RV and + biomarkers
Utilization of Thrombolysis

What are we Thinking?

In-hospital Mortality

Why Treat Sub Massive Elevated Risk PE

- PE and unresolved RV dysfunction at discharge
- 8-times more recurrent PE
- 4-times the mortality rate
- Quicker resolution of symptoms
- Less utilization of ICU
- Decreased need for therapy advancement
- Accelerated discharge?
- Accelerated return to asymptomatic state

Treatment of Higher Risk PE

What else can be done for Massive and sub-massive PE’s?

- IVC filters
- Embolectomy
- Surgery

Meta-Analysis Demonstrated Promise of CDT

<table>
<thead>
<tr>
<th>Major Complications</th>
<th>Clinical Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.4% (CI: 1.9%, 4.3%)</td>
<td>86.5% (CI: 82.2%, 90.2%)</td>
</tr>
</tbody>
</table>

Pharmaco-Mechanico Thrombolysis Step by Step

- Make the diagnosis and clinical decision consistently
- PERT team or other consistent algorithmic mechanism
- Hospital Environment may dictate options ie Tertiary vs community
- HAVE a STEMI like protocol to get patients to the to the correct environment
- Catheter vs EKOS institutional preference since there is a lack of randomized data and cost considerations
Risk vs Benefit (So Decrease the Risk of the Procedure)

<table>
<thead>
<tr>
<th>Risk</th>
<th>Mitigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic Bleeding</td>
<td>Proper pt selection</td>
</tr>
<tr>
<td>Local Bleeding</td>
<td>BP control</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>Ultrasound guided access</td>
</tr>
<tr>
<td>Overdosing of Lytic</td>
<td>Proper transfer techniques</td>
</tr>
<tr>
<td>Not being able to handle the need</td>
<td>Sedation</td>
</tr>
<tr>
<td>for advancing therapy</td>
<td>Catheter skills vs Swan</td>
</tr>
<tr>
<td></td>
<td>Monitor physiologically and stop when improved</td>
</tr>
<tr>
<td></td>
<td>Proper Consultations in T, surg and transfer</td>
</tr>
<tr>
<td></td>
<td>agreements with tertiary care if needed</td>
</tr>
</tbody>
</table>

Get the Patient Back from the Edge

Catheter Directed Thrombolysis

TPA: Catheter Directed Thrombolysis

- Don’t exceed 1 mg/hr total dose and limit time (24-48 hr)
  - 0.01 mg/kg/hr (max 1.0 mg/hr) => bleeding infrequent
- Minimize length of time of infusion
  - Longer exposure => more potential for bleeding and errors
- Lower time with concomitant heparin

MAPPET 3 trial
- N = 256
- Pulmonary hypertension or RV dysfunction without hypotensions
- Primary end points in hospital death or escalation of Rx
- Standard 100 mg dose and heparin vs heparin alone
- No difference in major bleeding

MOPPET Open label trial
- N = 121
- Ill pts = submassive elevated risk
- Half dose = 10mg bolus and 40 mg infusion
- No increased in excessive bleeding
- Decreased long-term pulmonary hypertension

tPA Dosing (non EKOS) Catheter Directed Thrombolysis

Ultrasound accelerated thrombolysis

EKOS EkoSonic® Mach 4e Endovascular System

5.4 F Drug Delivery Catheter

Ultrasound Core wire
Bilateral EKOS 12 CM in Place

Ultrasound-Assisted CDT
- ULTIMA (n=59): Randomized Trial*
  - Dose per-catheter: 1 mg/hr x 5 hr, then 0.5 mg/hr x 10 hr
  - Safety: No major bleeding (10% minor bleeding), no ICH
  - Efficacy: 24 hr RV/LV reduced by 27% (beat controls)
  - Full-dose heparin
- SEATTLE-II (n=150): Single-Arm Prospective Study**
  - Dose: Fixed dose 24 mg (1 mg/hr unilat; 2 mg/hr bilat)
  - Safety: 10% major bleeds (one GUSTO-3 bleed, no ICH)
  - UFH – PTT 40-60

OPTALYSE PE Trial
- 101 patients randomized: 1 of 4 dosing schemes
  - With LMWH or subtherapeutic-dose heparin
- No non-lysed control group (so any “efficacy” observed could just be due to heparin & time)
- Overall 4% patients had major bleeds, 2% ICH
  - 1 ICH attributed to CDT, one to systemic lysis

GROUPS
<table>
<thead>
<tr>
<th>GROUP 1</th>
<th>GROUP 2</th>
<th>GROUP 3</th>
<th>GROUP 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOSE</td>
<td>4-8 mg</td>
<td>4-8 mg</td>
<td>6-12 mg</td>
</tr>
<tr>
<td>over 2h</td>
<td>over 4h</td>
<td>over 6h</td>
<td>over 6h</td>
</tr>
<tr>
<td>RV/LV change</td>
<td>-24.0%</td>
<td>-22.5%</td>
<td>-20.3%</td>
</tr>
<tr>
<td>Miller index</td>
<td>-5.5%</td>
<td>-9.2%</td>
<td>-14.0%</td>
</tr>
<tr>
<td>Major bleeds</td>
<td>0 (0%)</td>
<td>1 (3.7%)</td>
<td>1 (3.6%)</td>
</tr>
<tr>
<td>ICH bleeds</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Why we lowered the dose
(PEITHO Trial: TNK (Tenectaplasoe))
- n = 1006 patients
- mean age 70 yrs
- 12 countries in Europe and Israel
- included patients with confirmed PE, an abnormal RV on echocardiography or CT, and a positive troponin I or T test result
- randomized blinded to therapy plus placebo or heparin plus full dose weight-adapted bolus of tenectaplasoe
- combined primary and secondary endpoint from any cause or hemodynamic collapse after seven days

Results:
- primary and pooled RRR of 16% if treated with tenectaplasoe and heparin, compared with the heparin-only group (0.4% in the tenectaplasoe group vs 6.4% in the placebo group, p < 0.01)
- a significant increase in major hemorrhage (including intracranial hemorrhage), particularly evident among elderly patients aged >75y
- major bleeding was significantly increased with tenectaplasoe, 4.5% vs 1.9% in the placebo group (p < 0.05)
- subgroup analysis by age, in the >75y group RRR was 32% and the risk of stroke almost 2%

When Are You Done With Lytic?
- Effects
  - Hemodynamic improvement
  - PA pressures
  - HR
  - Supplemental O2 requirement
  - Repeat CTPA for “locked lung”
- Bleeding
  - Groin
  - Oral
  - Other

Summary

• Develop a program and know your results
• Help develop the data
• Try to maximize benefit
• Try to minimize risk
• If uncomfortable get the patient to a higher level institution