Intravenous Thrombolytic Therapy for PE: Does it work acutely?

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Disclosures

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Entity</th>
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<tbody>
<tr>
<td>Consultant</td>
<td>Diagnostica Stago, Genentech, Siemens HealthCare, Portola Pharmaceuticals</td>
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<td>Advisory Board</td>
<td>Pfizer, Janssen Pharmaceuticals, Portola, Boehringer-Ingelheim</td>
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<tr>
<td>Grant Recipient</td>
<td>NIH, Diagnostica Stago, Siemens Healthcare, Janssen Pharmaceuticals</td>
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PE Mortality

ICOPER Registry
- 2454 PE
- 108 massive PE (SBP<90)

Quantification of Risk

EMPEROR
1880 Patients with confirmed PE:
- Hypotension: 3%
- RV hypokinesis on TTE: 12%
- Troponin (+): 23%
- BNP/NT-proBNP (+): 11%
- Aggregate: 35% (661/1880) with ≥1 high risk marker
- Fibrinolysis: 2% (45/1880) overall
  9% (3/58) hypotensive patients

Does IV thrombolysis help acutely?

- Patients in cardiac arrest?
- Patients who are unstable but not in cardiac arrest?
- Patients who are stable, with submassive PE?
- When other options (e.g. CDT) are available?
Thrombolytics for PE

**Alteplase (t-PA)**
- FDA Approved
- $T_{1/2} = 4-6$ min.
- 100 mg IV (15 mg bolus followed by 85 mg) over a 2-hour infusion.

**Tenecteplase**
- Not FDA Approved
- $T_{1/2} = 20-24$ min. (130 min. final clearance)
- Bolus dosing

<table>
<thead>
<tr>
<th>Weight</th>
<th>Dose</th>
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<tbody>
<tr>
<td>&lt;60</td>
<td>30mg</td>
</tr>
<tr>
<td>60-69</td>
<td>35mg</td>
</tr>
<tr>
<td>70-79</td>
<td>40mg</td>
</tr>
<tr>
<td>80-89</td>
<td>45mg</td>
</tr>
<tr>
<td>≥90</td>
<td>50mg</td>
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</tbody>
</table>

Does IV thrombolysis help patients in cardiac arrest?

Thrombolysis for Cardiac Arrest

  - Case Series to assess outcomes of thrombolysis during CPR for cardiac arrest due to PE
  - ROSC and survival to hospital discharge successful in 4/6 cases (66.7%)
  - CPR after thrombolysis for 15-90 minutes

- **Abu-Laban RB, et al. NEJM. 2002;246(20):1522-1528.**
  - Double blind RCT to evaluate effect of rt-PA during CPR in adults with undifferentiated PEA
  - 233 Out of hospital cardiac arrests
  - No difference in survival with thrombolysis
  - 32 minutes of CPR prior to tPA
  - 1/42 had PE on autopsy

  - Double blind RCT to determine whether the use of tenecteplase during CPR can improve survival in adults with witnessed out of hospital arrest.
  - 1050 Out-of-hospital cardiac arrests
  - No difference in ROSC or survival with thrombolysis
  - 18 minutes prior to tenecteplase

Does IV thrombolysis help patients who are unstable but not in cardiac arrest?

High Risk/Massive PE

Thrombolysis vs. Heparin

- Trials including hemodynamically unstable patients
  - Significant decrease in recurrent PE or death
    - 12% vs. 9%

- Trials excluding hemodynamically unstable patients
  - No significant difference in recurrent PE or death
    - 5% vs. 5%

Does IV thrombolysis help patients who are stable, with submassive PE?
There is one population of patients we’ve known about for nearly two decades who do seem to benefit from IV thrombolysis - and that is patients with large PE causing hemodynamic instability.

Patients with PE and hypotension have a >15% mortality rate, with most deaths coming in the first 24 hours, and many coming in the first hour.

While there has only been one randomized trial focusing on patients with hemodynamically unstable PE, with an n of 8, a meta-analysis of trials revealed that the mortality benefit of thrombolysis seemed to be limited to patients with hemodynamic instability.

Christopher Kabrhel, 11/20/2013
**Submassive PE**

**PEITHO**

- **Purpose:**
  - To investigate the benefit and safety of thrombolysis (Tenecteplase) versus placebo for normotensive patients with intermediate risk PE.

- **Randomized Trial**
  - double blind
  - placebo controlled
  - 1006 patients

**PEITHO Conclusions**

- Tenecteplase significantly reduced the incidence of death or hemodynamic collapse in patients with intermediate-risk PE.
- Tenecteplase significantly increased the risk of major bleeding and intracranial hemorrhage.
- The benefit from tenecteplase may be limited to a population <75 years old.

**Intravenous Thrombolysis**

**TOPCOAT**

- **Purpose:**
  - To investigate whether thrombolysis (Tenecteplase versus placebo) improves functional outcomes and quality of life for normotensive patients with intermediate risk PE.

- **Randomized Trial**
  - double blind
  - placebo controlled
  - 83 patients

**Hospital Resource Utilization**

**TOPCOAT**

<table>
<thead>
<tr>
<th>Adverse outcome</th>
<th>PLACEBO</th>
<th>TENECTEPLASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL UNIQUE PATIENTS</td>
<td>13</td>
<td>30%</td>
</tr>
<tr>
<td>Poor functional capacity</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Low perception of wellness</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>Two of the above</td>
<td>7</td>
<td>16%</td>
</tr>
<tr>
<td>All three of the above</td>
<td>1</td>
<td>2%</td>
</tr>
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</table>

Proportion free of any adverse outcome:

- 63% (Placebo) vs 85% (Tenecteplase), p=0.017
TOPCOAT

Conclusion

Patients with submassive pulmonary embolism who were treated with tenecteplase were more likely to have a good health related quality of life at three months.

PEITHO

<table>
<thead>
<tr>
<th>Condition</th>
<th>Tenecteplase (n=506)</th>
<th>Placebo (n=499)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Non-intracranial major bleeding</td>
<td>12 (2.4)</td>
<td>6 (1.5)</td>
<td>0.026</td>
</tr>
<tr>
<td>Severe</td>
<td>16</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>16</td>
<td>6</td>
<td></td>
</tr>
<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>Hemorrhagic</td>
<td>10</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>2</td>
<td>0</td>
<td></td>
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</table>

Overall Benefit/Risk of IV Thrombolysis

Meta-Analyses


Meta-Analysis

Hemodynamically stable patients with submassive PE

Chatterjee et al, JAMA, 2014

Meta-Analysis

Table 2. Absolute Risk Ratios of Outcomes of Major Interest

Chatterjee et al, JAMA, 2014
Meta-Analysis

Marti et al, Eur Heart J 2014

• Conclusion:
  – Thrombolytic therapy reduces total mortality in patients with submassive PE.
  – However, findings were not significant when studies enrolling high-risk (i.e. massive) PE were excluded from analysis.

European Heart Journal Meta-Analysis

MOPPET

• 121 Patients with signs and symptoms of PE plus:
  – CTPA: involvement of > 70% thrombus in ≥2 lobar or a main PA
  – V/Q: ventilation perfusion mismatch in ≥2 lobes.

• “Safe Dose” 50 mg IV tPA:
  – 10-mg bolus followed by infusion of 40 mg over 2 hours.

Sharifi, Am J Cardiology, 2013

No patient in either group had bleeding

Does IV thrombolysis help when other options (CDT) are available?

PERT Treatment

IV vs. Catheter Directed Thrombolysis

Major bleeding rates for catheter directed thrombolysis (3.6%) are similar to young, patients treated with IV thrombolysis in PEITHO.

Engelburger et al, Eur Heart Journal, 2013
Is it possible to lower the bleeding risk of patients by changing the dose of lytic given. This study is suggestive, and looks at chronic Right heart strain, but the results are encouraging especially with regards to the fact that no patient who received half dose thrombolysis had a bleeding complication.

Christopher Kabrhel, 11/20/2013
Summary

- Thrombolysis may be underused

- Thrombolysis can benefit:
  - Patients in cardiac arrest when PE is suspected
  - Patients with massive PE
  - Select patients with Submassive PE
    - Even when other approaches (e.g. CDT) are available

Thank You

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