Just Bust a Move: The Role of Alteplase in Cardiac Arrest and Pulmonary Embolus

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Outline
• Case
• Background
• Clinical Question
• Review of Evidence
• Conclusions

Learning Objectives
• To review the evidence behind thrombolytic use in cardiac arrest and pulmonary embolism
• To determine the optimal dose and regimen for alteplase for a patient in cardiopulmonary arrest due to a clinically suspected pulmonary embolism

Case
• ID: RC, 44yo male
• HPI:
  – Jan. 12 - RCMP found pt unresponsive after call from concerned friend:
    • empty bottles of oxycodone, zopiclone, clonazepam, diazepam, olanzapine, left wrist laceration, suicide note
    • Intubated, admitted to ICU
    – Jan. 14 - extubated, had a psych consult

Case
• PMH:
  – PTSD, Depression, GAD, ADHD, Bipolar disorder, Personality Disorder, previous OD Christmas 2005
• SH:
  – Lives with partner of 14 years, “rough” relationship
• Allergies:
  – NKA

Case
• Medications PTA:
  – Diazepam 10mg daily
  – Sertraline 50mg qhs
  – Lansoprazole 30mg daily
  – Clonazepam 1mg bid
  – Olanzapine 2.5mg qhs, 2.5mg prn
  – Zopiclone 7.5mg qhs
  – Divalproex 250mg qam, 750mg qhs
  – Oxycodone 5mg q6h prn
**Case**

- **Meds in Hospital:**
  - Heparin 5000 units sc q12h
  - ICU PRN orders:
    - Acetaminophen
    - Diazepam
    - Haloperidol
    - Morphine
    - Ipratroprium
    - Salbutamol

**Case Drug-Related Problems**

- RC is in cardiac arrest and would benefit from advanced cardiac life support
- RC is in cardiac arrest from a possible massive pulmonary embolus, and may benefit from receiving thrombolytic therapy
- RC is at risk from experiencing excess sedation secondary to receiving too much benzodiazepine, and would benefit from reassessment of his sedation drug therapy

**Case - Code Blue**

<table>
<thead>
<tr>
<th>Time</th>
<th>Pertinent Vitals</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:48</td>
<td>HR 89, GCS14-3, RR 22, BP 55/20</td>
<td></td>
</tr>
<tr>
<td>9:50</td>
<td></td>
<td>Infused</td>
</tr>
<tr>
<td>9:53</td>
<td></td>
<td>Naloxone 0.4mg</td>
</tr>
<tr>
<td>9:55</td>
<td>HR 43, BP 55/20</td>
<td>Atropine 1mg</td>
</tr>
<tr>
<td>10:06</td>
<td>HR 33</td>
<td>Atropine 1mg</td>
</tr>
<tr>
<td>10:12</td>
<td>HR &lt; 30</td>
<td>Atropine 1mg, Norepi infusion at 20mcg/min</td>
</tr>
<tr>
<td>10:14</td>
<td>HR 60</td>
<td>Alteplase 100mg iv bolus</td>
</tr>
<tr>
<td>10:16</td>
<td>BP not palpable, pulse not palpable</td>
<td></td>
</tr>
<tr>
<td>10:22</td>
<td>CPR stopped - still asystole - CPR resumed</td>
<td></td>
</tr>
<tr>
<td>10:26</td>
<td>CPR stopped, code called</td>
<td></td>
</tr>
</tbody>
</table>

Note: Multiple vasopressor boluses were given before Norepi infusion was started

**Goals of Therapy**

- Enable the return of spontaneous circulation
- Reduce mortality
- Prevent bleeding complications

**Background - Pulmonary Embolism (PE)**

- Potentially fatal disorder - death can occur within minutes of symptom onset
  - 65-95% mortality in PE patients requiring CPR
- Etiology - Virchow’s Triad:
  - Alteration in blood flow (stasis)
  - Endothelial injury
  - Hypercoagulable state
- Combinations of these factors leads to thrombus formation, and subsequent PE
**Background - PE Pathophysiology**

- Adherens
- von Willebrand factor
- Platelet aggregation
- Collagen/fibrin

**Background - PE Symptoms**

- Sudden onset of:
  - Dyspnea
  - Tachypnea
  - Pleuritic chest pain
  - Cough, hemoptysis
- Massive PE is a PE with **shock**, severe hypoxia, and/or right-sided heart failure
- DDx includes MI and pneumonia - objective testing required for diagnosis

**Background - PE Diagnosis**

- Tests such as D-Dimer and V/Q scans not practical when a patient is in cardiac arrest
- Quick diagnostic tools exist, such as the Wells Score:

  - **Wells Score**:
    - Clinical features of deep vein thrombosis
    - Recent prolonged immobilization or surgery
    - Active cancer
    - History of deep vein thrombosis or pulmonary embolism
    - Hemoptysis
    - Resting heart rate > 100 beats per minute
    - New alternative explanations for acute shortness of breath or chest pain

  - Score 5-6 = high probability; 2-4 = moderate probability; 0-1 = low probability

**Background - Massive PE Treatment**

- IV Heparin:
  - Weight-based iv bolus followed by infusion (LGH nomogram)
  - Target PTT 60-120s
- Fibrinolysis:
  - Unclear evidence

**Background - Alteplase**

- Common thrombolytic used sometimes in ischemic stroke, acute MI and PE
- Doses used:
  - Our PDTM says:
    - Acute MI: 1.5mg iv bolus, then 0.75mg/kg over 30min, then 0.5mg/kg over 60min (Max dose = 100mg)
    - PE: 100mg iv infusion over 2h
    - Acute Ischemic Stroke: 0.9mg/kg (Max dose = 90mg) given 10% as bolus, and 90% over 60min
  - 50mg bolus over 15min does not increase bleeding rates compared to a 100mg/2hr infusion (n=87)

**PICO Question**

- **P** In a 44yo male patient in cardiac arrest believed to be due to a massive pulmonary embolism, is thrombolytic therapy **better than placebo** at reducing mortality?
Literature Search

- Databases searched:
  - Pubmed, Embase, Medline, Google Scholar, and bibliographies of relevant articles
- Search terms:
  - Alteplase, thrombolysis, bolus, cardiopulmonary arrest, massive pulmonary embolism, cardiac arrest
- Found:
  - 3 RCT's
  - 1 Cochrane review
  - 2 Retrospective studies
  - Multiple reviews, 1 case series

What do the Guidelines say?6

- If cardiac arrest occurs and massive PE is strongly suspected, a 50mg iv bolus dose of alteplase should be given
- If patient is deteriorating at 30min, administer another 50mg iv bolus
- But what is this recommendation based on?

Ruiz-Bailen - Design

- Case series from an ICU in Spain
- N = 6
- All patients had cardiac arrest secondary to fulminant pulmonary embolism (FPE)
- All patients received two 50mg iv boluses of alteplase, separated by 30min
- Mortality = 2/6

Ruiz-Bailen - Results

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age at admission</th>
<th>Cardiac arrest:</th>
<th>Initial dose of alteplase</th>
<th>Time of injection of alteplase (min)</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>75</td>
<td>Mass pulmonary embolism</td>
<td>50mg bolus</td>
<td>After 3 mins</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>80</td>
<td>FPE</td>
<td>50mg bolus</td>
<td>After 2 mins</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>75</td>
<td>FPE</td>
<td>50mg bolus</td>
<td>After 3 mins</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>80</td>
<td>FPE</td>
<td>50mg bolus</td>
<td>After 2 mins</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>75</td>
<td>FPE</td>
<td>50mg bolus</td>
<td>After 3 mins</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>80</td>
<td>FPE</td>
<td>50mg bolus</td>
<td>After 2 mins</td>
<td>20</td>
</tr>
</tbody>
</table>

Ruiz-Bailen - Limitations

- Case series:
  - Low level of evidence
  - Prone to selection bias
- Merely hypothesis generating
- No control group
- 2/6 patients had hemorrhage at injection sites
Abu-Laban Trial - Design

- Stats:
  - N = 230 to show a 9.3% survival rate increase
  - 233 patients enrolled
- Postmortem findings for all patients who received autopsies (n=42):
  - 9 had acute MI (21.4%)
  - 4 had hemorrhage (9.5%)
  - 1 had pulmonary embolism (2.4%)

Abu-Laban Trial - Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Type</th>
<th>Pharmacologic Treatment</th>
<th>P-value (Chi-sq)</th>
<th>Absolute Difference</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROSC</td>
<td></td>
<td>Alteplase</td>
<td>0.02</td>
<td>15 (9.3%)</td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td>Death</td>
<td>0.44</td>
<td>32 (17.3%)</td>
<td></td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td>MI</td>
<td>0.03</td>
<td>77 (40.8%)</td>
<td></td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td>Hemorrhage</td>
<td>0.00</td>
<td>23 (12.8%)</td>
<td></td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td>Stroke</td>
<td>0.00</td>
<td>2 (1.1%)</td>
<td></td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td>Other</td>
<td>0.00</td>
<td>2 (1.1%)</td>
<td></td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td>Unknown</td>
<td>0.00</td>
<td>2 (1.1%)</td>
<td></td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td>N/A</td>
<td>0.00</td>
<td>2 (1.1%)</td>
<td></td>
</tr>
</tbody>
</table>

Abu-Laban Trial - Limitations

- Autopsies showed only 2.4% of patients died from pulmonary embolism
- Patients were out-of-hospital cardiac arrests, only 77 patients made it to hospital - limits applicability to our patient
- Study was powered only to show a LARGE effect - possible Type I error of missing a smaller effect

Abu-Laban Trial - Application

- Thrombolytic therapy should not be used for all patients with PEA, as there is no significant increase in survival
  - Thrombolysis should be considered on a case-by-case basis
- Thrombolytic therapy during PEA is not associated with significantly higher rates of bleeding complications
- PEA has a very poor prognosis
Thrombolytic Therapy for Pulmonary Embolism (Review)

Dong BR et al.
Cochrane Library 2009; Issue 3

Cochrane Review - Design

<table>
<thead>
<tr>
<th>Studies</th>
<th>8 RCTs, N = 679</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatments</td>
<td>Any type of thrombolytic (alteplase, urokinase, streptokinase) compared to heparin alone or placebo or surgical intervention</td>
</tr>
<tr>
<td>Participants</td>
<td>All patients with signs/symptoms of PE, confirmed by pulmonary angiography, V/Q scan, or other validated instrument</td>
</tr>
<tr>
<td>1st endpoints</td>
<td>All-cause mortality, survival time, PE recurrence, major and minor hemorrhagic complications, quality of life, healthcare costs</td>
</tr>
<tr>
<td>2nd endpoints</td>
<td>Markers of hemodynamic improvements, thrombolysis, pulmonary hypertension, coagulation parameters, post-thrombotic syndrome</td>
</tr>
</tbody>
</table>

Cochrane Review - Results

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis (n=396)</th>
<th>Heparin (n=283)</th>
<th>Data analysis</th>
<th>Weight</th>
<th>Data ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alteplase (n=396)</td>
<td>1.95</td>
<td>1.95</td>
<td>5.245</td>
<td>0.71</td>
<td>1.01</td>
</tr>
<tr>
<td>Streptokinase (n=283)</td>
<td>0.06</td>
<td>0.06</td>
<td>0.0</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>Urokinase (n=283)</td>
<td>0.08</td>
<td>0.08</td>
<td>0.0</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>Urokinase (n=283)</td>
<td>0.08</td>
<td>0.08</td>
<td>0.0</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>All trials (n=679)</td>
<td>0.08</td>
<td>0.08</td>
<td>0.0</td>
<td>0.86</td>
<td></td>
</tr>
</tbody>
</table>

Cochrane Review - Limitations

- Only included patients with confirmed PE - patients in cardiac arrest do not have time for a diagnostic test
- Only included hemodynamically stable patients:
  - Only one study done to date comparing thrombolysis vs heparin alone in hemodynamically unstable patients

Cochrane Review - Application

- Definitive evidence for the efficacy of thrombolytic therapy in acute pulmonary embolism is lacking
- Major bleeding events with thrombolytic therapy are similar to standard therapy (heparin)
- More blinded trials are needed to correctly answer this debate

Streptokinase and Heparin versus Heparin Alone in Massive Pulmonary Embolism: A Randomized Controlled Trial

Jerjes-Sanchez C, et al.
Jerjes-Sanchez - Design

<table>
<thead>
<tr>
<th>Design</th>
<th>Single-center, open RCT</th>
</tr>
</thead>
</table>
| Treatment | Gp 1: 1,500,000 IU Streptokinase iv over 1h  
Gp 2: No initial treatment |
| Both groups received heparin iv 10,000U bolus followed by infusion |
| Inclusion | > 15 y/o, strong clinical suspicion of PE |
| Exclusion | Previous PE, contraindication to thrombolytic, <3 occluded segments on V/Q Scan, recent hemorrhage, ICH, neurologic or major surgery |
| 1° endpoint | Endpoints not clearly identified |

Jerjes-Sanchez - Results

- **N** = 8, all with massive PE and cardiogenic shock
- 4 patients in streptokinase group, 4 in heparin:
  - **Mortality (%)**
    - Group Streptokinase + Heparin: 4/4 (100%)
    - Group Heparin: 0/4 (0%)
  - **P = 0.02**
  - Study terminated after discussion with ethics committee

Jerjes-Sanchez - Limitations

- Extremely small sample size
- Poorly described methodology:
  - No endpoint description
  - No statistical analysis description
  - No blinding
  - Cardiogenic shock was not in inclusion criteria

Conclusion

- In a patient presenting with PEA, thrombolytic therapy will likely have no benefit on mortality
- If massive PE is strongly suspected as the cause of the PEA, thrombolysis may be considered, and will not increase bleeding risks
- A 50mg bolus over 15min can safely be given as an alternative to the PDTM recommendation in a code situation, with a repeated bolus after 30min (although safety data on 2nd bolus is sparse)

References


Questions?
**TROICA Trial - Design**

- **Stats:**
  - N = 1000 to show 7% relative improvement in outcome with a power of 90%
  - 1650 patients recruited
- **Baseline characteristics all similar EXCEPT:**
  - P-value
  - Transcetyple Group
  - Placebo Group
  - P-value
  - Mortality on day 1
  - Mortality on day 2
  - Risk of death on day 3

**TROICA Trial - Results**

**TROICA Trial - Limitations**

- Differences in rates of suspected PE
- Patients were out-of-hospital cardiac arrests - limits applicability to our patient
- No patients received heparin
- Study used tenecteplase, not alteplase

**TROICA Trial - Application**

- Thrombolytic therapy should not be used for cardiac arrest with simply a cardiac cause, as there is no benefit in mortality
- There is a significantly higher rate of ICH in patients who receive thrombolysis for cardiac arrest