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

- Jan. 15:
  - BP =105/55, HR =85, RR =24, $Sa0_2$ =95%, T =36.6
  - Seemingly well in am, got up to go to bathroom, and **collapsed** on way back
  - Hypoxic, hypotensive, bradycardic
  - Code blue called

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

Goals of Therapy

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

Case - Code Blue

Time	Pertinent Vitals	Interventions
9:40	HR 89, GCS14-3, RR 22, BP 55/20	
9:50		Intubated
9:53		Naloxone 0.4mg
9:55	HR 43, BP 55/20	Atropine 1mg
10:06	HR 33	Atropine 1mg
10:12	HR < 30	Atropine 1mg, Norepi infusion at 20mcg/min
10:14	HR 60	**Alteplase 100mg iv bolus**
10:16	BP not palpable, pulse not palpable	
10:22	CPR stopped - still asystole - CPR resumed	
10:26	CPR stopped, code called	

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

Background - Pulmonary Embolism (PE)

- Potentially fatal disorder - death can occur within minutes of symptom onset
  - 65-95% mortality in PE patients requiring CPR[1,2]
- Etiology - Virchow's Triad:[3]
  - Alteration in blood flow (stasis)
  - Endothelial injury
  - Hypercoagulable state
- Combinations of these factors leads to thrombus formation, and subsequent PE

Background - PE Pathophysiology[3]

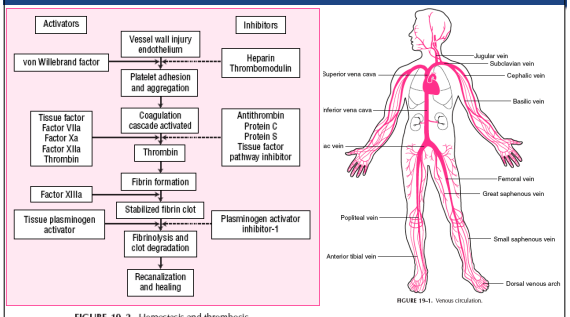


FIGURE 19–2. Hemostasis and thrombosis.

FIGURE 19–1. Venous circulation.

Background - PE Symptoms[3]

- 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[3,4]

- 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:

Pretest Probability of PE	
Clinical features of deep vein thrombosis	3.0
Recent prolonged immobility or surgery	1.5
Active cancer	1.0
History of deep vein thrombosis or pulmonary embolism	1.5
Hemoptysis	1.0
Resting heart rate > 100 beats per minute	1.5
No alternative explanation for acute shortness of breath or chest pain	3.0

Score ≥6 = high probability; 2–6 = moderate probability; ≤1.5 = low probability

Background - Massive PE Treatment

- IV Heparin:[4]
  - Weight-based iv bolus followed by infusion (LGH nomogram)
  - Target PTT 60-120s
- Fibrinolysis:
  - Unclear evidence

Background - Alteplase

- Common thombolytic used sometimes in ischemic stroke, acute MI and PE
- Doses used:
  - Our PDTM says:
    - Acute MI:15mg 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)[7]

PICO Question

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

Literature Search

- Databases searched:
  - Pubmed, Embase, MedLine, Google Scholar, and bibliographies of relevant articles
- Search terms:
  - Alteplase, thombolysis, 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?

Thrombolysis with Recombinant Tissue Plasminogen Activator during Cardiopulmonary Resuscitation in Fulminant Pulmonary Embolism: A Case Series

Ruiz-Bailen M, et al.

Resuscitation 2001; 51: 97-101

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

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Sex	Woman	Male	Male	Male	Male	Woman
Age	45	28	34	73	76	56
Medical history	Cardiac valve disease	Neoplasm of pancreas	Fracture of patella	None	None	Protein S deficit
Type de CA	EMD	EMD	Asystole	EMD	Asystole	EMD
Start of CPR	Immediate	After 5 min	After ⩾10 min	Immediate	Immediate	Immediate
rt-PA Administration delay (after CPR initiation, min)	60	30	30	15	Immediate	15
rt-PA Regimen	50 mg in bolus + 50 mg after 30 min[a]	50 mg in bolus + 50 mg after 30 min[a]	50 mg in bolus	50 mg in bolus + 50 mg after 30 min[a]	50 mg in bolus + 50 mg after 30 min[a]	50 mg in bolus + 50 mg after 30 min[a]
Total dosage of rt-PA (mg)	100	100	100	100	100	100
Total time of CPR (min)	70	45	90	30	5	40
Neurologic sequelae	None	Death	Death	None	None	None
Post-CPR complications	Haemorrhage at injection sites	None	None	None	Haemorrhage at injection sites, UDH	None
PE diagnosis	Scintigraphy	Necropsy	Necropsy	Pulmonary arteriography	Scintigraphy	Scintigraphy
Other treatments	Heparin, dopamine	Heparin	None	Heparin, domapine	Heparin, epinephrine	Heparin, dopamine
Evolution	After 1 year, alive without sequelae	Death	Death	After 1 year, alive without sequelae	After 1 year, developed stroke	After 6 months, alive without sequelae

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

Tissue Plasminogen Activator in Cardiac Arrest with Pulseless Electrical Activity

Abu-Laban RB et al.
NEJM 2002; 346(20): 1522-8

Abu-Laban Trial - Design

Design	Double-blind, multicenter, RCT
Treatment	Grp 1: Alteplase 50mg iv bolus over 15 min Grp 2: Placebo iv bolus over 15 min Both groups received ACLS for at least 15min after treatment
Inclusion	> 16 yo, PEA > 1min, no palpable pulse for 3 minutes during CPR, all patients were intubated
Exclusion	DNR order, trauma, **overdose**, pregnancy, history of ICH or stroke, hypothermia, hemorrhage, renal dialysis, asphyxia, airway compromise as a cause of CA, cardiac tamponade
1° endpoint	Survival to hospital discharge
2° endpoints	Return of spontaneous circulation (ROSC), length of hospital stay, neurologic outcome, hemorrhage

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 4. OUTCOMES.

VARIABLE	TISSUE PLASMINOGEN ACTIVATOR GROUP (N=117)	PLACEBO GROUP (N=116)	ABSOLUTE DIFFERENCE (95% CI)*	P VALUE
			%	
Return of spontaneous circulation — no. (%)	25 (21.4)	27 (23.3)	−1.9 (−12.6 to +8.8)	0.85
Median maximal duration — min†	28	11	+17 (−4 to +26)	0.45
Mean maximal duration — min†	395	182		
Died at scene — no. (%)	73 (62.4)	74 (63.8)	−1.4 (−13.8 to +11.0)	0.93
Transported to hospital — no. (%)	39 (33.3)	38 (32.8)	+0.5 (−11.6 to +12.6)	0.96
Arrived with pulse	19 (16.2)	10 (8.6)	+7.6 (−1.0 to +16.5)	0.12
Arrived without pulse	20 (17.1)	28 (24.1)	−7.0 (−17.4 to +3.4)	0.24
Enrolled at hospital and died in emergency department — no. (%)	5 (4.3)	4 (3.4)	+0.9 (−5.2 to +6.9)	0.99
Survived to hospital admission — no. (%)	7 (6.0)	6 (5.2)	+0.8 (−5.9 to +7.8)	0.99
Major hemorrhage — no. (%)	2 (1.7)	0	+1.7 (−1.7 to +6.4)	0.50
Minor hemorrhage — no. (%)	1 (0.9)	1 (0.9)	0.0 (−4.1 to +4.1)	0.99
Length of hospital stay — days				
Median	0.4	0.5	−0.1 (−0.4 to +2.5)	0.62
Mean	6.3	0.5		
Survival to hospital discharge — no. (%)	1 (0.9)‡	0§	+0.9 (−2.6 to +4.8)	0.99

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.

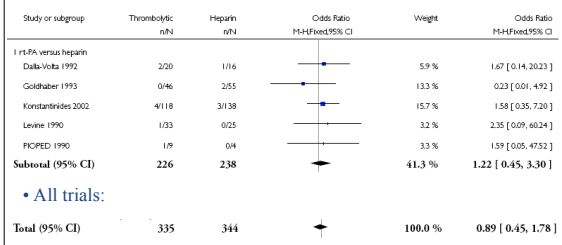
Cochrane Library 2009; Issue 3

Cochrane Review - Design

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

Cochrane Review - Results

- Alteplase trials:



- All trials:

Total (95% CI)	335	344	100.0 %	0.89 [0.45, 1.78]

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.

Journal of Thrombosis and Thrombolysis 1995; 2: 227-9

Jerjes-Sanchez - Design

Design	Single-center, open RCT
Treatment	Grp 1: 1,500,000 IU Streptokinase iv over 1h Grp 2: No initial treatment Both groups received heparin iv 10,000U bolus followed by infusion
Inclusion	> 15 yo, 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
2° endpoints	

Jerjes-Sanchez - Results

- N = 8, all with massive PE and cardiogenic shock
- 4 patients in streptokinase group, 4 in heparin:

Group	Streptokinase + Heparin	Heparin
Mortality (%)	0/4 (0%)	4/4 (100%)

- 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

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10. Jerjes-Sanchez C, Ramirez-Rivera A, de Lourdes Garcia M, et al. Streptokinase and heparin versus heparin alone in massive pulmonary embolism: a randomized controlled trial. Journal of Thrombosis and Thrombolytics 1995; 2: 227-9.

Questions?

Thrombolysis during Resuscitation for Out-of-Hospital Cardiac Arrest

Bottiger BW, et al
NEJM 2008; 359: 2651-62
TROICA Trial

TROICA Trial - Design

Design	Double-blind, multicenter, RCT
Treatment	Grp 1: Tenecteplase 30-50mg (dose based on weight) iv bolus Grp 2: Placebo iv bolus Both groups received ACLS for at least 30min after treatment
Inclusion	Witnessed out-of-hospital cardiac arrest (CA) of presumed cardiac origin, ACLS within 10 min of collapse
Exclusion	Suspected non-cardiac cause of CA, known internal bleeding, neurologic impairment, pregnancy, coagulation disorders, hypersensitivity, or increased risk by investigator discretion
1° endpoint	30-day survival
2° endpoints	Hospital admission, return of spontaneous circulation (ROSC), 24-hr survival, survival to hospital discharge, neurologic outcome, ICH, major bleeding outcomes

TROICA Trial - Design

- Stats:
  - N = 1000 to show 7% relative improvement in outcome with a power of 90%
    - 1050 patients recruited
- Baseline characteristics all similar EXCEPT:

Variable	Tenecteplase Group (N=525)	Placebo Group (N=525)	P Value
	no./total no. (%)		
Presumed cause of cardiac arrest			<0.01
Acute myocardial infarction	377/504 (74.8)	343/501 (68.5)	
Primary arrhythmia	65/504 (12.9)	82/501 (16.4)	
Pulmonary embolism	30/504 (6.0)	55/501 (11.0)	
Other cardiac cause	32/504 (6.3)	21/501 (4.2)	

TROICA Trial - Results

Table 4. Outcomes.

Outcome	Tenecteplase Group (N=525)	Placebo Group (N=525)	Relative Risk (95% CI)	P Value
	no./total no. (%)			
Primary end point				
30-Day survival	77/525 (14.7)	89/525 (17.0)	0.87 (0.65–1.15)	0.36
Secondary end points				
Return of spontaneous circulation	283/515 (55.0)	279/511 (54.6)	1.01 (0.90–1.13)	0.96
Hospital admission	281/525 (53.5)	289/525 (55.0)	0.97 (0.87–1.09)	0.67
24-Hr survival	158/517 (30.6)	171/514 (33.3)	0.92 (0.77–1.10)	0.39
Survival to hospital discharge	78/517 (15.1)	90/514 (17.5)	0.86 (0.65 –1.14)	0.33
Neurologic outcome[a]				0.69
Good cerebral performance	41/86 (47.7)	45/96 (46.9)	1.02 (0.75–1.38)	
Moderate cerebral disability	13/86 (15.1)	9/96 (9.4)	1.12 (0.88–1.42)	
Severe cerebral disability	10/86 (11.6)	16/96 (16.7)	1.02 (0.86–1.21)	
Coma	14/86 (16.3)	18/96 (18.8)	0.99 (0.90–1.08)	
Brain death	8/86 (9.3)	8/96 (8.3)	1.00	
Safety end points				
Symptomatic intracranial hemorrhage	4/518 (0.8)	0/514	8.93 (0.48–165.45)	0.13
Any intracranial hemorrhage	14/518 (2.7)	2/514 (0.4)	6.95 (1.59–30.41)	0.006
Major nonintracranial hemorrhage	40/517 (7.7)	33/514 (6.4)	1.21 (0.77–1.88)	0.48
Ischemic stroke	4/518 (0.8)	3/514 (0.6)	1.32 (0.30–5.88)	1.00

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