Critical Review Form
Therapy

Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion

Lancet 1993; 341:501-511

Objective: **To determine "whether thrombolysis followed by anticoagulation was superior to anticoagulation alone in reversing echocardiographic evidence of right-ventricular dysfunction associated with PE" (p. 507). Additionally, they sought to understand whether thrombolysis improves pulmonary tissue perfusion more rapidly than heparin alone and whether thrombolysis lowers the incidence of clinically suspected recurrent PE.**

Methods: **Between November 1988 and July 1991 at one (?) U.S. hospital patients >18 years old with signs or symptoms of PE within the preceding 14-days with PE confirmed by high probability V/Q scan or pulmonary angiogram within the last 24-hours were randomized to either heparin (5000 unit bolus then 1500 units/hr to maintain PTT 1.5 – 2.5-times the upper limit of normal) or rt-PA 100mg IV over 2-hours followed by heparin 1000 units/hour if PTT < 2x normal to target PTT 1.5 – 2.5x upper limit of normal. All patients had to have baseline echo and post-treatment echo at 3-hours and24-hours.**

Exclusion criteria included major internal bleeding in the previous 6-months, intracranial or intraspinal disease, operation or biopsy in the preceding 10-days, occult blood in stool, Hct < 28%, platelet < 100,000/µL, systolic BP > 200 or diastolic BP > 110 mmHg, severely impaired hepatic function, pregnancy, endocarditis, hemorrhagic retinopathy or any concurrent condition considered to limit survival to less than 1 month.

Echocardiograms were assessed by two individuals blinded to the subject's allocation arm. They assessed RV wall motion (normal, mild, moderate, or severely hypokinetic), tricuspid regurgitation, and qualitative RV cavity size.

Patients were followed for 14-days (or longer if they remained hospitalized). Adverse outcomes assessed included death, clinically suspected recurrent PE, or major bleeding. The trial had 80% power with 2-sided α= 0.05 to detect a change in RV wall motion improvement from 30% (heparin alone) to 60% (rt-PA) assuming 25% inadequate echo if 50 subjects were randomized to each arm.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. "After eligibility was established, patients were randomized to rt-PA (alteplase) followed by heparin or to heparin alone by opening the appropriate consecutively numbered sealed envelope. Separate, non-blinded, open-label treatment assignments for each hospital were generated by permuted block random number sequences". (p. 508)
2.	Was randomization concealed (blinded)?	It is not clearly stated whether patients or clinicians were blinded to allocation assignment. However, outcome assessment for one outcome (RV wall motion abnormality) was blinded. "Baseline, 3h, and 24h echocardiograms were coded to prevent identification of treatment and timing in relation to therapy". (p. 508)
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "Data were analyzed by randomization assignments ('intention-to-treat')". (p. 509)
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. "101 patients had similar baseline characteristics" (Table 1) (p. 509)
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	Uncertain. Not clearly stated who was and was not blinded.
2.	Were clinicians aware of group allocation?	Uncertain.
3.	Were outcome assessors aware of group allocation?	Yes. See A-2 above.
4.	Was follow-up complete?	No loss to follow-up is reported. However, several heparin-only patients received off-protocol rt-PA as cross-over subjects.

II.	What are the results (answer the questions posed below)?	
1.	How large was the treatment effect?	• 101 subjects (mean age 58.5) were randomized after 1.5 days on heparin into rt-PA (46) or heparin (55). None had SBP < 90mmHg. • 80% had PE diagnosed by V/Q scan. • 89% had three adequate echos with the following findings at 3h. RV wall motion worse / same or better rt-PA 2 / 29 Heparin 10 / 38 Therefore, **NNT with rt-PA = 7 (95% CI 4 - ∞) to prevent one patient from having worsening RV wall.** Similarly, RV wall motion at 24h worse / same or better rt-PA 1 / 40 Heparin 8 / 40 Therefore, **NNT = 7 (95% CI 6 – 56) to prevent one patient from having worsening of RV wall function at 24h.** • General linear model demonstrated ↓RV end-diastolic area in t-PA but not heparin patients (p=0.01) with most of reduction occurring in the first 3h. • Among 36 patients (18 rt-PA, 18 heparin) with baseline RV hypokinesis 89% of rt-PA improved vs. 44% of heparin (with 6% and 28% worsening respectively). • Perfusion improved significantly more in rt-PA group (14.5% improvement vs. 1.5% in heparin

<table>
<tr>
<td>1.</td>
<td>How large was the treatment effect?</td>
<td>

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89% had three adequate echos with the following findings at 3h.

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worse</th><th>same or better</th></tr>
<tr><td>rt-PA</td><td>2</td><td>29</td></tr>
<tr><td>Heparin</td><td>10</td><td>38</td></tr>
</table>
Therefore, NNT with rt-PA = 7 (95% CI 4 - ∞) to prevent one patient from having worsening RV wall.

Similarly, RV wall motion at 24h
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<tr><th></th><th>worse</th><th>same or better</th></tr>
<tr><td>rt-PA</td><td>1</td><td>40</td></tr>
<tr><td>Heparin</td><td>8</td><td>40</td></tr>
</table>
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Limitations

1) **No CONSORT-like diagram to assess exclusions and drop-outs.**

2) **No definitions for exclusion criteria (intracranial or intraspinal disease, severely impaired hepatic function) and failure to include trauma as an exclusion criteria.**

3) **Failure to assess time to treatment as a prognostic variable or time to event as an analytic technique (Cox proportional hazards) although few timed events to assess.**

4) **Failure to elucidate role of Genentech sponsors/donors with the data analysis.**

5) **Use of high probability V/Q scan as diagnostic standard when V/Q is neither 100% sensitive nor 100% specific.**

6) **No clear statement of blinding other than in the echocardiographer outcome assessors.**

7) **No patient-oriented evidence that matter (POEM's) such as death, symptom control or escalation of therapy, hospital LOS.**

8) **Limited external validity to ED settings since t-PA was not administered until 1.5-days after the heparin was started.**

9) **No clear statement of patient location, level of care, initial illness severity, or hospitals from where they were recruited.**

Bottom Line

In select PE patients (see multiple exclusion criteria), rt-PA [100mg over 2h administered up to 1.5 days after heparin is initiated] can significantly decrease 24-hour RV wall motion worsening (NNT = 7) compared with heparin alone. The subset with baseline RV wall motion abnormality may benefit the most from thrombolysis and should be the focus of future investigations. Future trials need to assess patient-oriented outcomes.