CLINICAL INVESTIGATIONS

Safety and Efficacy of Reduced-Dose Versus Full-Dose Alteplase for Acute Pulmonary Embolism: A Multicenter Observational Comparative Effectiveness Study*

Background

- Pulmonary embolism (PE) remains a significant cause of morbidity and mortality.
- Systemic thrombolysis improves outcomes in patients with PE but is associated with the risk of hemorrhage.
- There is little data showing that the reduced-dose regimen (50 mg) of alteplase can improve RV dysfunction and lung perfusion defects.
- Given the small number of studies and the variability of the trial size, additional information is needed to inform clinicians on the optimal thrombolytic dose regimen.

AIM of the study

To compare baseline characteristics, outcomes, and complications in patients with PE treated with full- or reduced-dose alteplase regimens.

Methods (I)

- Retrospective multicenter observational study.
- Patients were included if they were 18 years old or older and treated with systemic alteplase for PE.
- Patients were classified as receiving either full dose alteplase if they received 100 mg IV over 2 hours, or reduced dose alteplase if they received 50 mg IV over 2 hours or 10 mg bolus over 1 minute followed by 40 mg over 2 hours.
- Primary outcomes for this study were all-cause and PE-related mortality or hemorrhage within 7 days of alteplase administration.

Methods (II)

- Secondary outcomes included shock index at 8 hours after alteplase administration defined as HR divided by systolic blood pressure (SBP), 30-day and 1-year all-cause mortality, and ICU and hospital length of stay.
- Other key secondary outcomes included changes in systolic blood pressure (SBP), heart rate (HR), respiratory rate (RR), need for supplemental oxygen, noninvasive ventilation, mechanical ventilator, and vasopressor use before and after alteplase.
- Due to the observational nature of this study, propensity score (PS) weighting was used to adjust for imbalances of baseline characteristics between reduced- and full-dose patients.

Results (I)

- A total of 284 patients were included in the retrospective analysis: 98 were treated with the full-dose and 186 with the reduced-dose alteplase regimen.
- At baseline, PE was classified as massive in 97 (34.5%) and submassive in 184 (65.5%) cases.
- Patients receiving the full-dose regimen were more likely to have a massive PE relative to those in the reduced-dose group (56.1% vs. 23%), whereas the reduced-dose group had a higher proportion of patients with a submassive PE (77.0% vs. 43.9%), $p < 0.001$.
- There were no clinically significant differences between the groups in terms of age and gender, comorbidities, or most baseline laboratory values.

Results (II)

- After the PS weighting, the full-and reduced-dose alteplase groups appeared well balanced with regard to key baseline differences in the unweighted groups.
- In the weighted cohort, there was no difference between the groups in 7-day all-cause (5.6% in full-dose vs. 8% in reduced-dose, p = 0.45) or PE-related (4% in full-dose vs. 4.2% in reduced-dose, p = 0.93) mortality, nor in 30-day or 1-year mortality.
- Improvements in SBP, HR, shock index, RR, and supplemental oxygen requirements were noted in both groups.
- The need for rescue interventions (catheter-directed procedures or surgical embolectomy) was infrequent and did not differ between groups.
- There were no significant differences between the groups in the discharge destination, ICU or hospital LOS, or readmission rates.

TABLE 2. (*Continued*)

Outcomes of Patients With Pulmonary Embolism Treated With Systemic Thrombolysis

	Unweighted Cohort				Weighted Cohort		
	Total (*n* = 284)	Full Dose (*n* = 98)	Reduced Dose (*n* = 186)	*p*	Full Dose (*n* = 98)	Reduced Dose (*n* = 186)	*p*
Hospital LOS (d), median (IQR)	4.3 (2.9, 6.9)	5.1 (3.3, 7.8)	3.9 (2.8, 6.3)	0.011	5.0 (3.1, 7.0)	4.3 (2.9, 7.0)	0.87
ICU LOS (d), median (IQR)	1.6 (1.0, 2.8)	1.8 (1.1, 3.3)	1.5 (1.0, 2.5)	0.091	1.6 (0.9, 2.8)	1.7 (1.0, 2.6)	0.89
Discharge destination				0.008			0.13
Home	214 (79.3%)	61 (68.5%)	153 (84.5%)		74.2%	82.5%	
LTACH/SNF	44 (16.3%)	23 (25.8%)	21 (11.6%)		22.9%	12.5%	
Hospice/comfort care	12 (4.4%)	5 (5.6%)	7 (3.9%)		2.9%	5.0%	
Readmission	26 (9.2%)	13 (13.3%)	13 (7.0%)	0.081	12.0%	6.6%	0.18
Pulmonary embolism-related mortality within 7 d	11 (3.9%)	6 (6.1%)	5 (2.7%)	0.15	4.0%	4.2%	0.93
All-cause mortality within 7 d	19 (6.7%)	9 (9.2%)	10 (5.4%)	0.22	5.6%	8.0%	0.45
All-cause mortality within 30 d	24 (8.5%)	14 (14.3%)	10 (5.4%)	0.010	8.6%	8.0%	0.86
All-cause mortality within 1 yr	44 (15.5%)	21 (21.4%)	23 (12.4%)	0.045	14.2%	17.3%	0.50

HR = heart rate, beats per minute, IQR = interquartile range, LOS = length of stay, LTACH = long-term acute care hospital, NIV = noninvasive ventilation, RR = respiratory rate, respirations per minute, SBP = systolic blood pressure, mm Hg, SNF = skilled nursing facility.

Results (III)

- In the unweighted cohort, the overall rates of hemorrhagic complications were significantly lower in the reduced-dose group than in the full-dose group (13% vs. 24.5%, respectively, $p = 0.014$).
- The differences persisted in the PS weighted cohort (1.3% in reduced-dose vs. 7.1% in full-dose for major, $p = 0.067$ and 12.8% in reduced dose vs. 17.2% in full-dose, $p = 0.32$ for minor) but did not reach statistical significance.
- Additional hemorrhage risk factors were identified in the majority of patients: 91.7% of them were systemically anticoagulated at the time of the complication development, with anticoagulation levels being in the supratherapeutic range in 37.5% of cases; 31.3% of patients underwent an invasive procedure close to the time of alteplase administration.

TABLE 4.
Hemorrhagic Complications

		Unweighted Cohort			Weighted Cohort		
	Total ($n = 284$)	Full Dose ($n = 98$)	Reduced Dose ($n = 186$)	p	Full Dose ($n = 98$) (%)	Reduced Dose ($n = 186$) (%)	p
Hemorrhage, any	48 (17.0%)	24 (24.5%)	24 (13.0%)	0.014	24.7	15.4	0.12
Minor	37 (13.1%)	17 (17.4%)	20 (10.8%)	0.17	17.2	12.8	0.32
Major extracranial	8 (2.8%)	6 (6.1%)	2 (1.1%)	0.022	7.1	1.3	0.067
Intracranial	3 (1.1%)	1 (1.0%)	2 (1.1%)	0.99	0.5	1.5	0.46
Among those with any hemorrhage							
Invasive procedure	15 (31.3%)	10 (41.7%)	5 (20.8%)	0.12	39.9	16.1	0.053
Systemic anticoagulation	44 (91.7%)	22 (91.7%)	22 (91.7%)	0.99	94.9	86.8	0.32
Supratherapeutic anticoagulation[a]	18 (37.5%)	8 (33.3%)	10 (41.7%)	0.55	34.6	45.6	0.42

[a]Supratherapeutic anticoagulation = activated partial thromboplastin time > 2.5 times of control value or heparin activity > 0.7 units/mL.

Conclusions

- Consistent with previous publications, in this trial, reduced-dose alteplase results in outcomes similar to the full-dose regimen but is associated with a lower risk of bleeding.
- There is need to further evaluate the comparative effectiveness, safety, and costs of the reduced- and full-dose alteplase regimens and to compare them to the catheter-based interventions and third-generation thrombolytic agents.
- Individualized approach, with treatment algorithms taking into account patient presentation, comorbid conditions, response to the initial treatment, and risks and benefits of reperfusion therapy may result in best outcomes.