A Retrospective Evaluation of Pulmonary Embolism And Thrombolysis in patients admitted to the Intensive Care Unit (REPEAT-ICU)

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Introduction

- Pulmonary embolism (PE) is the third most common cause of cardiovascular death worldwide after stroke and heart attack, and often requires admission to the intensive care unit (ICU).[1]
- PEs are classified as high risk (massive), intermediate-low and intermediate-high risk (submassive) or low risk based on their physiological impact and risk of complications.[2]
- The course of treatment is determined by PE classification and patient-specific factors.
- Systemic thrombolysis is a well recognized treatment modality for high risk PEs; however, uncertainty exists in guidelines and current literature surrounding the most appropriate treatment for intermediate risk PEs.[3]
- Intensivists in the ICU at both Royal Jubilee Hospital (RJH) and Victoria General Hospital (VGH) have adopted an informal order set to deliver extended infusion thrombolysis (range dose 24-54 mg over 24 hours) for selected cases, titrated according to pro-thrombin time (PTT) and fibrinogen levels over 24 hours. This strategy is preferred for intermediate risk PE by some prescribers because of a perception that it has a lower risk of clinically important bleeding.

Study Objective

- This study was done to determine the frequency, safety and efficacy of all thrombolysis strategies used in Victoria ICU patients diagnosed with PE, with a special interest in extended infusion thrombolysis for intermediate risk PE.

Methods

Design:
Retrospective chart review with a convenience sample size of 90 patients.

Inclusion Criteria
- Patients admitted to Victoria ICUs (i.e., VGH or RJH) between January 2017 and November 2022
- Patients admitted to the ICU with a primary diagnosis of PE
- Patients > 18 years old

Statistical Analysis:
Primary and secondary outcomes were expressed using descriptive statistics with data presented as means and standard deviations (SD) or numbers and percentages.

Outcomes Measures:
- **Primary Outcome:** Proportion of patients within each of the PE risk categories who received systemic thrombolysis (conventional dose, half dose, extended infusion), catheter-directed thrombolysis or both as well as the average dose and time of thrombolytic administration.
- **Secondary Outcome:** Safety and efficacy of outcomes based on overall pharmacotherapeutic management and disease severity, especially with respect to intermediate risk PE.
- *Note: The pulmonary embolism severity index (PESI) score was used to describe 30-day mortality at baseline and at 48 hours.*

Results

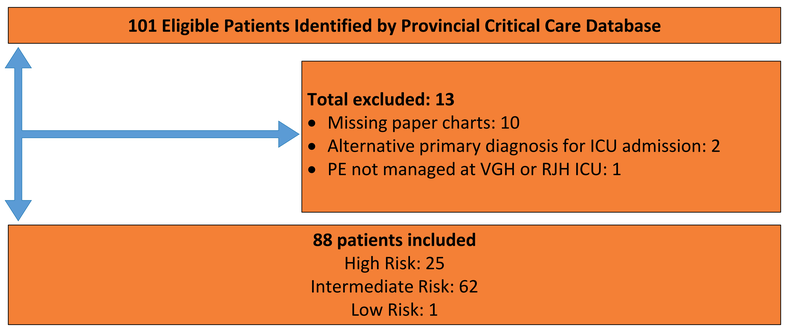

Figure 1. Patient inclusion

Results (continued)

Table 1. Baseline Characteristics

Characteristics	Overall population (N = 88)	Received thrombolysis (N = 50)	Received NO Thrombolysis (N = 38)
Age (years)	61.3 ± 16.7	57.8 ± 16.1	66.0 ± 16.9
Male no. (%)	45 (51.1)	22 (44)	23 (60.5)
Cancer History no. (%)	23 (26.1)	9 (18)	14 (36.8)
History of intracranial hemorrhage no. (%)	4 (4.5)	0 (0)	4 (10.5)
History of bleeding no. (%)	39 (44.3)	13 (26)	26 (68.4)
Previous VTE (DVT or PE) no. (%)	17 (19.3)	5 (10)	12 (31.6)
Ischemic stroke within 3 months no. (%)	3 (3.4)	1 (2)	2 (5.4)
History of intracranial or intraspinal surgery or serious head trauma no. (%)	5 (5.7)	2 (4)	3 (7.9)
Recent Surgery or Trauma within 30 days no. (%)	26 (29.5)	7 (14)	19 (50)
Baseline PESI Score	111.09 ± 42.68	103.2 ± 43.4	121.5 ± 39.9

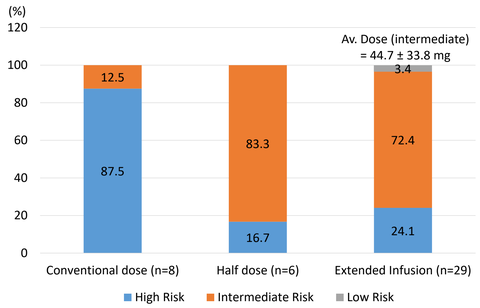

Figure 2. Mode of systemic thrombolysis
*catheter-directed thrombolysis not represented; extended infusion average time for intermediate risk PE ranged between 23.2 and 26.3 hours

Table 2. Legend for mode of thrombolysis

Types of thrombolysis	Definitions
Conventional Dose	100 mg over 2 hours (including 20 mg bolus as part of 100 mg)
Half Dose	50 mg over 2 hours (including 10 mg bolus as part of 50 mg)
Extended infusion	Infusion > 2 hours

Table 3. Informal Order Set Use

Risk Category	Informal order set frequency N (%)
Intermediate [N=21]	16 (76.1)
High Risk [N=7]	3 (42.9)
Low Risk [N=1]	0

Table 4. Efficacy Outcomes for Intermediate Risk PE *(high and low risk patients were not included in this table)*

Mode of thrombolysis	Method of thrombolytic administration	Efficacy Outcomes: Death from any cause N (%)	Death due to PE N (%)	Length of stay in ICU (days)	Need for Intubation N (%)	Time to Extubation (days)	48-hour PESI score N (%)	Pulmonary Hypertension N (%)
Systemic thrombolysis	Conventional dose [N=1]	0	0	0.8 ± 0.0	0	N/A	**Low Risk:** 1 (100)	0
	Half dose [N= 5]	0	0	2.0 ± 0.6	0	N/A	**Low Risk:** 4 (80) **Intermediate Risk:** 1 (20)	3 (100)
	Extended infusion [N=21]	1 (4.8)	1 (4.8)	3.33 ± 2.9	0	N/A	**Low Risk**: 15 (71.4) **Intermediate Risk:** 2 (9.5) **High Risk:** 4 (19.0)	10 (47.6)
Anticoagulation – no thrombolysis [N=28]		0	0	2.5 ± 3.0	3 (10.7)	2.3 ± 2.6	**Low Risk**: 9 (32.1) **Intermediate Risk:** 7 (25) **High Risk**: 12 (42.9)	3 (10.7)

Table 5. Safety Outcomes Based on Overall Pharmacotherapeutic Management

Mode of thrombolysis	Method of thrombolytic administration	Safety Outcomes: Minor bleeding N (%)	Moderate bleeding N (%)	Severe/Life-threatening bleeding N (%)	Death due to bleeding N (%)	Thrombolytic-induced Coagulopathy *(PTT >35s/<25s, Fibrinogen >4g/L/<2g/L)* N (%)
Systemic thrombolysis	Conventional dose [N=8]	5 (62.5)	0	1 (12.5)	0	6 (75)
	Half dose [N=6]	3 (50)	2 (33.3)	2 (33.3)	0	3 (50)
	Extended infusion [N=29]	16 (55.2)	3 (10.3)	7 (24.1)	1 (3.4)	20 (67.0)
Anticoagulation – no thrombolysis [N=35]		16 (45.7)	0	5 (14.3)	0	N/A

Discussion

- Systemic thrombolysis prescribed as extended infusion was most commonly utilized in patients with intermediate risk PE.
- Intensivists elected to use systemic thrombolysis in over 70% of intermediate risk PEs. This is a significant finding as guidelines recommend thrombolytic therapy be reserved for those patients who develop hemodynamic instability.[2,4,5]
- Prescribing strategies amongst intensivists for intermediate risk PE were heterogeneous but, on average, the thrombolytic dose administered for extended infusion was 44.7 mg over approximately 24 hours which remains within the range dose specified on the informal order set.
- In those patients who received extended infusion, half of the patients experienced minor bleeding, seven patients (24%) experienced severe/life-threatening bleeds and one patient experienced death due to bleeding. Overall, patients who received the extended infusion had higher rates of bleeding compared to those who did not receive extended infusion (i.e., anticoagulation alone and conventional dosing).
- Minor bleeding rates were similar between the conventional dose and extended infusion groups (62.5 vs. 55%). Moderate to severe bleeding rates were higher in the extended infusion group compared to the conventional dose group (34% vs. 12.5%) and the only death from bleeding was found in the extended infusion group. Therefore, the data indicates that extended infusion may not be as benign a mode of thrombolytic administration as initially perceived.
- Biochemically determined coagulopathy (i.e., abnormal PTT and fibrinogen levels) was similar between thrombolytic strategies, suggesting that thrombolytic-induced bleeding was similar between the groups.
- Patients who did not receive systemic thrombolysis in the presence of intermediate risk PE had a higher rate for intubation, a higher 48-hour PESI score but a reduced length of stay in the ICU. Therefore, systemic thrombolysis may reduce intubation and improve 48-hour PESI Score but at the risk of increased bleeding and longer ICU stay even in the extended infusion group.
- When extended infusion was prescribed for the management of intermediate risk PE, the informal order set was utilized for the administration of systemic thrombolysis in over 70% of the cases. Therefore, we hypothesize that the existence of an informal order set may have inadvertently promoted the practice of running extended infusion in the absence of supporting evidence.

Limitations

- Small sample size and unbalanced treatment groups made it difficult to compare bleeding risks between treatment groups with precision.
- Retrospective analysis was based on written and dictated chart notes which may have contained incomplete information.

Conclusion

- Intensivists at VGH and RJH frequently used the informal order set to prescribe extended infusion thrombolysis for the management of intermediate risk PE in the absence of supporting evidence.
- Extended infusion thrombolysis was the most commonly prescribed thrombolytic strategy in the presence of intermediate risk PE and had the highest risk of clinically important bleeding. Therefore, extended infusion may not be as benign as initially perceived.
- The use of systemic thrombolysis may be effective in improving outcomes in patients with intermediate risk PE (i.e., improve 48-hour PESI score and reduce intubation rate) but may be associated with higher rates of bleeding and longer length of stay in ICU. Therefore, thrombolytic therapy and its method of administration should be carefully considered on an individual basis, taking into account the patient's comorbidities and risk of bleed.
- We would discourage the use of extended infusions and the use of the informal order set as a thrombolytic strategy for intermediate risk PE until more robust and supportive data are available.

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References available on request