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Safety and efficacy of catheter directed thrombolysis (CDT) in elderly with pulmonary embolism (PE)

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ABSTRACT

Introduction Acute pulmonary embolism (PE) remains a common cause for morbidity and mortality in patients over 65 years. Given the increased risk of bleeding in the elderly population with the use of systemic thrombolysis, catheter-directed therapy (CDT) is being increasingly used for the treatment of submassive PE. Nevertheless, the safety of CDT in the elderly population is not well studied. We, therefore, aimed to evaluate the safety of CDT in our elderly patients.

Methods We conducted a retrospective observational study of consecutive patients aged ≥ 65 years with a diagnosis of PE from our Pulmonary Embolism Response Team database. We compared the treatment outcomes of CDT versus anticoagulation (AC) in elderly. Propensity score matching was used to construct two matched cohorts for final outcomes analysis.

Results Of 346 patients with acute PE, 138 were ≥ 65 years, and of these, 18 were treated with CDT. Unmatched comparison between CDT and AC cohorts demonstrated similar in-hospital mortality (11.1% vs 5.6%, $p=0.37$) and length of stay (LOS) (3.81 vs 5.02 days, $p=0.5395$), respectively. The results from the propensity-matched cohort mirrored results of the unmatched cohort with no significant difference between CDT and AC in-hospital mortality (11.8% vs 5.9%, $p=0.545$) or median LOS (3.76 vs 4.21 days, $p=0.77$), respectively.

Conclusion In this observational study using propensity score-matched analysis, we found that patients >65 years who were treated with CDT for management of acute PE had similar mortality and LOS compared with those treated with AC. Further studies are required to confirm these findings.

Key messages

- ▶ Is it safe to use catheter-directed therapy (CDT) in the elderly?
- ▶ Acute pulmonary embolism (PE) remains a common cause of morbidity and mortality in patient over 65. Given the increased risk of bleeding in the elderly population with the use of systemic thrombolysis, catheter directed thrombolysis (CDT) is being increasingly used for the treatment of submassive PE.
- ▶ The safety of CDT in the elderly population is not well studied.
- ▶ Patients ≥ 65 who were treated with catheter directed thrombolysis for management of acute PE had similar mortality and length of stay to patients treated with anticoagulation.

of treatment of intermediate-risk PE with a rapid reduction in right ventricle (RV) to left ventricle ratio and mean pulmonary artery systolic pressure with an excellent safety profile in relatively younger cohort.⁷⁻¹⁰ In this observational study, we evaluated the safety of CDT therapy in the elderly cohort compared with standard AC first with univariate analysis and then using propensity score matching. We hypothesise that CDT therapy is not inferior in safety (bleeding risk, mortality) compared with that of AC in elderly cohort.

METHODS

We retrospectively reviewed the data of 346 consecutive patients with acute PE collected from September 2017 to June 2019 in the Temple University Hospital Pulmonary Embolism Response Team (PERT) registry with approved review board protocol 26021. We then selected all patients aged ≥ 65 years and excluded patients who underwent systemic thrombolysis, mechanical and surgical embolectomy. We then compared the clinical outcomes of patients treated with CDT

INTRODUCTION

Elderly patients aged ≥ 65 years are at an increased risk for pulmonary embolism (PE) and also have high mortality rates and bleeding risk after systemic anticoagulation (AC) compared with younger patients.¹⁻³ Moreover, treatment with systemic thrombolysis is associated with higher risk of major bleeding (13% vs 3%) and intracranial haemorrhage (1.4% vs 0.5%).¹⁻⁶ Catheter-directed thrombolysis (CDT) is an effective method



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to those treated with AC therapy with univariate analysis and then with propensity matching.

The treatment decision to proceed with CDT or other interventions was made by a multidisciplinary PERT. Major bleeding was evaluated and defined using the International Society on Thrombosis and Hemostasis (ISTH) criteria.¹¹ The clinical outcomes included in-hospital mortality and hospital length of stay (LOS).

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Statistical analysis

Descriptive summary statistics are presented as mean values with SD for continuous variables and frequencies with percentages for categorical variables. Baseline characteristics were compared between the elderly CDT and AC cohorts using an independent two-sample t test or two-sample Wilcoxon rank-sum test for continuous variables and using a Pearson χ^2 test for categorical variables.

Clinical characteristics that were evaluated include age, race, body mass index (BMI), history of hypothyroidism, deep vein thrombosis (DVT), PE, malignancy, diabetes

mellitus, chronic obstructive pulmonary disease, cardio-pulmonary disease, recent surgery, current use of AC prior to admission, inferior vena cava filter, chronic kidney disease with and without need for renal replacement therapy, and PE severity by European Society of Cardiology (ESC) classification as low risk (1), intermediate-to-low risk (2), intermediate-to-high risk and high risk (4).⁴ There were two outcomes of interest: (1) in-hospital mortality and (2) LOS. The LOS was not censored for in-hospital mortality.

The association between patient characteristics and outcome was assessed using univariate logistic regression with OR and corresponding 95% CIs.

We used propensity scores to construct two matched groups for comparative outcomes analysis. In order to perform propensity scores matching, we excluded patients who had history of malignancy or recent surgery and patients who had a PE severity as defined by ESC classification of low risk (1), intermediate-to low risk (2) and high risk (4).

For outcome analysis, we compared elderly patients treated with CDT versus AC. Statistical analyses were conducted using Stata (V. 14.0).

Table 1 Baseline patient characteristics, univariate analysis and propensity matched groups

Column	Unmatched groups			Propensity matched groups		
	AC 108	CDT 18	P value	AC 17	CDT 17	P value
Age	75.5±7.99	73.8±6.19	0.329	77.6±7.89	73.7±6.35	0.121
Caucasian	19 (41.7%)	5 (27.8%)	0.464	2 (11.7%)	5 (29.4%)	0.286
BMI (kg/m ²)	28.8±8.51	33.8±7.66	0.024	30.4±12.2	33.9±7.9	0.340
Medical History						
Hypothyroidism	12 (11.2%)	3 (16.7%)	0.51	1 (5.9%)	3 (17.7)	0.287
DVT	15 (14.0%)	6 (33.3%)	0.043	4 (23.5%)	6 (35.3%)	0.452
PE	10 (9.4%)	5 (29.4%)	0.018	1 (5.9%)	5 (29.4%)	0.072
Malignancy	33 (30.8%)	0	0.006	–	–	–
Diabetes mellitus	39 (36.5%)	3 (16.7)	0.1	7 (41.2%)	3 (17.6%)	0.132
COPD	29 (27.4%)	2 (11.1%)	0.141	6 (35.3%)	1 (5.9)	0.034
Cardiopulmonary	46 (55.4%)	8 (53.3%)	0.881	8 (66.7%)	7 (50.0%)	0.391
Recent surgery	23 (21.5%)	0	0.029	–	–	–
AC use	11 (10.3)	1 (5.6%)	0.529	2 (11.8%)	1 (5.9%)	0.545
IVC filter	3 (2.8%)	2 (11.1%)	0.096	1 (5.9%)	2 (11.8%)	0.545
CKD	17 (15.9%)	2 (11.1%)	0.601	3 (17.7%)	2 (11.8%)	0.628
ESRD on RRT	4 (3.7%)	0	0.404	1 (5.9%)	0	0.31
PE severity (ESC)						
1	23 (21.5%)	0	<0.001	0	0	–
2	43 (40.2%)	0		0	0	
3	38 (35.5%)	18 (100%)		17(100%)	17(100%)	
4	3 (2.8%)	0		0	0	

Bold font indicates statistical significance

AC, anticoagulation; BMI, body mass index; CDT, catheter directed thrombolysis; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; ESC, European Society of Cardiology; ESRD, end-stage renal disease; IVC, inferior vena cava; PE, Pulmonary embolism; RRT, renal replacement therapy.

Table 2 Clinical descriptions of patients receiving CDT

Age	Gender	Admission oxygen requirement	PE category (ESC) Classification	DVT	CDT*	Survival to discharge	ISTH major bleeding	Discharge location
78	Female	BiPAP	Intermediate high	No	Bilateral 12 mg	Yes	Yes	SNF
75	Female	NRB	Intermediate high	Yes	Bilateral 16 mg	No	No	Deceased
84	Female	4 L/min	Intermediate high	Yes	Unilateral 20mg	Yes	No	SNF
79	Female	6 L/min	Intermediate high	Yes	Bilateral 12 mg	Yes	No	Home
77	Female	10 L/min	Intermediate high	No	Unilateral 6mg	Yes	No	Home
73	Male	6 L/min	Intermediate high	Yes	Bilateral; 12 mg	Yes	No	Home
73	Female	4 L/min	Intermediate high	Yes	Bilateral 12 mg	Yes	No	Home
69	Female	0 L/min	Intermediate high	Yes	Bilateral 12 mg	Yes	No	Home
68	Female	0 L/min	Intermediate high	No	Bilateral 12 mg	Yes	No	Home
67	Male	0 L/min	Intermediate high	Yes	Bilateral 24 mg	Yes	No	Home
66	Male	0 L/min	Intermediate high	No	Bilateral 24 mg	Yes	No	Home
65	Male	0 L/min	Intermediate high	-	Bilateral 24 mg	Yes	No	Home
66	Female	2 L/min	Intermediate high	Yes	Bilateral 12 mg	Yes	No	Home
71	Male	2 L/min	Intermediate high	Yes	Bilateral 12 mg	Yes	No	Home
76	Male	3 L/min	Intermediate high	Yes	Bilateral 24 mg	Yes	No	Home
76	Female	0 L/min	Intermediate high	No	Bilateral 12 mg	Yes	No	SNF
83	Male	2 L/min	Intermediate high	No	Bilateral 12 mg	No	No	Deceased
83	Male	2 L/min	Intermediate high	Yes	Unilateral 6 mg	Yes	No	SNF

*CDT details: unilateral versus bilateral catheter placement in the pulmonary artery catheters and total tPA dose.

BiPAP, bilevel positive airway pressure; CDT, catheter directed thrombolysis; DVT, deep vein thrombosis; ESC, European Society of Cardiology; ISTH, International Society on Thrombosis and Hemostasis; NRB, non-rebreather; PE, pulmonary embolism; SNF, skilled nursing facility; tPA, tissue plasminogen activator.

RESULTS

We identified 138 (39.9%) patients who were 65 years and older out of the 346 consecutive patients in the PERT database. The mean (SD) age was 75.3 (7.2) years, 56.5% were females, 19% were Caucasian. Among those identified, 108 (85.7%) patients were treated with AC and 18 patients (14.3%) with CDT. Baseline clinical characteristics of the patients are shown in [table 1](#).

Table 3 Bleeding complication, survival and follow-up for patients receiving CDT

CDT discharge outcome	n (%)
Bleeding after tPA*	
Gastrointestinal bleed	1 (5.6)
Survival at discharge	16 (88.9)
Outpatient follow-up†	12 (66.7)
Death from any cause within 30 days	2 (11.1)
Rehospitalisation within 30 days	0
Supplemental oxygen therapy at discharge	1 (5.6)

*Major bleeding was evaluated and defined using the International Society on Thrombosis and Hemostasis criteria.

†Four patient were outside referrals and followed up at their respective institutions.

CDT, catheter directed therapy; tPA, tissue plasminogen activator.

All 18 patients in the CDT cohort had intermediate-to-high risk (3) PE as compared with 38.7% of patients in the non-CDT cohort ($p < 0.001$). Baseline clinical characteristics of the CDT cohort are shown in [table 2](#). The overall mortality in the elderly cohort was 6.3%. All-cause mortality in CDT compared with AC cohorts was 11.1% and 5.6% respectively ($p = 0.37$).

Univariate analysis of clinical characteristics showed that patients treated with CDT compared with AC had significant comorbidities including BMI (28.8 vs 33.8, $p = 0.024$), histories of DVT (14% vs 33.3%, $p = 0.043$), PE (9.4% vs 29.4%, $p = 0.018$) or malignancy (30.8% vs 0%, $p = 0.006$), recent surgery (21.5% vs 0%, $p = 0.029$) and PE severity score ($p < 0.001$) ([table 1](#)).

In-hospital mortality was not different in the CDT cohort compared with the AC cohort (OR (95% CI) 2.15 (0.394 to 11.457), $p = 0.381$). The median LOS for the CDT vs AC cohort were 3.81 and 5.02 days respectively ($p = 0.540$).

Baseline characteristics for the propensity-matched cohort are listed in [table 1](#) and show no significant differences between the two groups, suggesting good-quality match.

The results in the propensity-matched cohort showed no difference for in-hospital mortality for the CDT group (5.88% vs 11.76%, $p = 0.545$). Additionally, the median



LOS for the CDT versus AC cohort were 3.76 and 4.21 days ($p=0.77$) after matching. Postprocedure adverse effect and outpatient follow-up information listed in [table 3](#).

DISCUSSION

In this study, elderly patients with mean age of 75 years with intermediate-risk PE were treated with CDT as compared with systemic AC. The CDT cohort had significantly higher comorbidities including BMI, histories of DVT, PE or malignancy, recent surgery and PE severity scores. Even with a more moribund patient population, there was no statistically significant difference when comparing in-hospital mortality ($p=0.545$) and LOS ($p=0.77$) among the two cohorts after propensity matching. There were two major bleeding events per ISTH criteria and two fatalities in the CDT cohort but all-cause mortality in CDT compared with AC cohorts was not statistically significant.

Optimal management remains uncertain for elderly patients ≥ 65 years as they have a higher 30-day and 90-day mortality rates of 14.2% and 20.8%, respectively, as well as higher risk of bleeding compared with younger patients (2.5% vs 0.9%).^{1 3 5 6}

Systemic thrombolysis is another intervention that is under investigation but is not recommended in the management of intermediate risk PE because the risk of life-threatening bleeding complications outweighs the benefits of therapy.^{4 12} The PEITHO trial is a large randomised control trial that found increased risk of major bleeding in a nonelderly cohort which offsets the benefits of therapy.⁵ A subgroup analysis of patients older than 65 years old had higher risk of bleeding events (12.93% vs 4.10%, $p<0.001$). There is limited published data on treatment options and associated morbidity and mortality for elderly patients with intermediate-risk PE using CDT therapy.

The mean age for our CDT cohort was 75 years whereas the average age in published clinical trials from ULTIMA, SEATTLE II, PERFECT and OPTALYSE were 59–63 years.^{7–10} In our CDT cohort, 10 patients (55.6%) were treated with total tissue plasminogen activator (tPA) dose of 12 mg. The remaining eight patients were treated with variable total doses ranging from 6 to 24 mg. The ULTIMA trial infused 10 mg of tPA per lung and SEATTLE II infused 24 mg tPA.^{7 8} The OPTALYSE trial had different regimens including 4 mg for 2 hours, 4 mg for 4 hours, 6 mg for 6 hours and 12 mg for 6 hours. Reported bleeding rates in published literature with CDT studies include up to 10% and ours was 5.6%.^{7 8 10} Each study used a different definition of bleeding.^{7 8 10}

We had two patient deaths that occurred 24 hours post-CDT procedure. In-hospital death for ULTIMA, SEATTLE II and OPTALYSE trials are zero, three patients and one patient, respectively.^{7 8 10} All these trials enrolled both low-risk PEs and high-to-intermediate risk PEs, while our study only included high-intermediate risk PEs.

The patient who experienced major bleeding in our CDT cohort was a 78-year-old woman who developed a diverticular bleed post-treatment that required transfusions and self-resolved without intervention.

Out of the two patients who expired, one was a 75-year-old woman that developed massive haemoptysis from right lower lob pulmonary artery rupture likely predisposed by her history of chronically elevated haemidiaphragm 3 hours after catheter placement.¹³ The other patient was an 83-year-old man who underwent CDT with a total tPA dose of 12 mg administered over 6 hours who deteriorated and subsequently had pulseless electrical activity arrest.

In our study, patients who survived were asymptomatic and had minimal oxygen dependence postprocedure with 15 out of 18 patients being oxygen-free at discharge. Most patients were discharged to home and had no 30-day readmission. At the follow-up, patients remained oxygen-free and had overall good functional status. Overall, there was greater than 93% survival rate with associated clinical improvement.

Some strengths of our study include collecting data on a patient cohort who are generally sicker with increased comorbidities. We demonstrate robust statistical matching using propensity score-matched analysis and univariate analysis for comparison between cohorts. A rapid assessment of patients by a PERT team is critical in elderly patients with acute PE. AC is the cornerstone management of these patients; however, if deterioration occurs despite AC therapy, CDT is a relatively safe and effective approach that rapidly restores RV function. We hope that multi-centre cohort studies from high-volume centres will allow for more reliable conclusions on the efficacy of CDT in treating acute PE in the elderly. Our results must be interpreted in context of the study limitations including a small size and retrospective data from a single academic tertiary medical centre.

CONCLUSION

This retrospective observational study shows that elderly patients have similar in-hospital mortality and LOS when treated with CDT versus anticoagulation alone. In elderly patients who have high-to-intermediate risk acute PE and are candidates for interventional therapy, CDT may be a safe alternative treatment modality. These findings will need to be confirmed in randomised controlled trial like Pulmonary Embolism Thrombus Removal With Adjunctive Catheter-Directed Therapy (PE-TRACT) trial.

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Contributors EH is the primary author, collected the data and is the guarantor of the article, taking responsibility for the integrity of the work as a whole from inception to published article. RA, MP, JSK collected the data. VL, KUL, RG, JH, KM, PR and GC helped write the manuscript. HZ conducted the statistical analysis. JP, RB, GC reviewed the imaging studies and also treated the patients who underwent catheter directed thrombolysis. JSK was a secondary coauthor, responsible for the study concept and helped write the manuscript.

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