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Outcomes of Catheter-Based Interventions for the Treatment of Intermediate to High-Risk Pulmonary Embolism in Patients With High Bleeding Risk: A Single-Centre Experience

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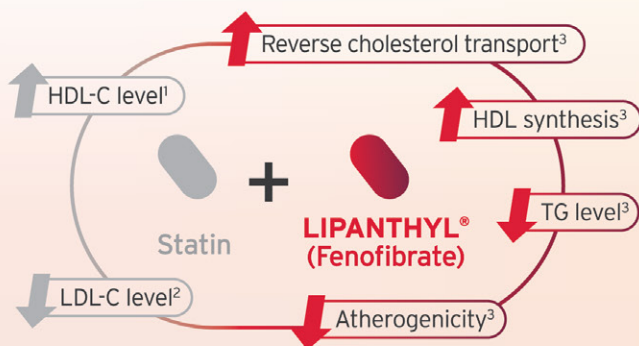
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AACE=American Association of Clinical Endocrinology; ACE=American College of Endocrinology; ASCVD=atherosclerotic cardiovascular disease; CV=cardiovascular; ECLIPSE-REAL=Effectiveness of Fenofibrate Therapy in Residual Cardiovascular Risk Reduction in the Real World; HDL=high-density lipoprotein; HDL-C=HDL cholesterol; LDL-C=low-density lipoprotein cholesterol; TG=triglyceride.

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Outcomes of Catheter-Based Interventions for the Treatment of Intermediate to High-Risk Pulmonary Embolism in Patients With High Bleeding Risk: A Single-Centre Experience

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Abstract

Background: Catheter-based reperfusion therapy is considered an alternative treatment for intermediate to high-risk pulmonary embolism (PE). These therapies can be divided into catheter-directed thrombolysis and catheter-based thrombectomy. High bleeding risk (HBR) were generally excluded from previous studies. Outcomes of these two treatment modalities in patients with high-risk PE are limited.

Method: This is a single centre retrospective cohort study of patients who were admitted for intermediate to high-risk PE and who were treated with catheter-based interventions due to contraindications for systemic thrombolysis. Baseline demographics, procedural details, clinical outcomes including 30-day PE-related mortality, and bleeding complications including blood transfusion and incidence of intracranial haemorrhage (ICH) were reported.

Result: 28 patients with acute PE (mean age 58 years) and contraindications for systemic thrombolysis were included in this study, of which 8 (28%) were high-risk. 14 patients (42.9% high and 57.1% intermediate-risk) were treated by aspiration thrombectomy (AT) and 14 (14.3% high and 85.7% intermediate-risk) by ultrasound-assisted catheter-directed thrombolysis (USCDT). There were 3 (10.7%) PE related mortality within 30 days. All of them were high-risk PE and in the USCDT arm. Overall incidence of moderate to severe bleeding was 41.7% (50% in AT and 21.4% in USCDT arm) and most of these patients required blood transfusion. The procedural time were 107.6 minutes for AT and 57.1 minutes for USCDT.

Conclusion: Catheter-based interventions with either AT or USCDT are viable treatment option for intermediate to high-risk pulmonary embolism in patients with high bleeding risk. AT was associated with lower mortality rate in high-risk patients but higher incidence of blood transfusion and longer procedural time.

Keywords: Pulmonary embolism, Ekosonic Endovascular system, Catheter-directed thrombolysis, Penumbra, Aspiration thrombectomy, Bleeding

Introduction

Acute pulmonary embolism (PE) is a common disease that is associated with significant

morbidity and mortality. In one local epidemiology study, the annual incidence of PE was reported to be 11.7 per 100 000 population, and the incidence increases with age with annual age specific incidence

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being 18.6 per 100 000 for those more than age of 65 in Hong Kong [1]. Despite the increase in incidence, the mortality associated with PE may be decreasing over time. This might be due to timely diagnosis and guideline-directed management with effective treatments [2].

In addition to anticoagulation, reperfusion therapy is recommended as a life-saving treatment in high-risk PE, and as a rescue therapy in intermediate PE [3]. Systemic thrombolysis and surgical embolectomy while being effective reperfusion therapies, are limited by their complications such as bleeding and high perioperative mortality [4–8]. Percutaneous catheter-based treatments are gaining popularity and are recommended as alternative options [3]. There are mainly two modalities of catheter-based therapy: catheter-directed thrombolysis (CDT) and catheter-based thrombectomy. CDT can be enhanced by equipping ultrasound probes inside the catheter to facilitate the delivery of the thrombolytic drugs. The ultrasound assisted catheter-directed thrombolysis (USCDT) has the theoretical advantages of reducing the thrombolytic dose and thus lowering risk of bleeding complications. There are many forms of catheter-based thrombectomy, and aspiration thrombectomy (AT) which removed the occlusive thrombus mechanically by suction is one of them. Different catheter-based treatments were evaluated in various prospective single-arm studies for their efficacy and procedural related complications including significant bleeding, and were proven to be efficacious and safe [9–11]. However, most of these studies excluded patients with high bleeding risk (HBR), and only a few retrospective studies included patients with high-risk PE. In this analysis, we will report the clinical outcomes of patients with intermediate to high-risk PE treated by one of these catheter-based therapies.

Methods

Study subjects

This is a retrospective cohort study drawing data from the New Territory West Cluster hospitals network in Hong Kong SAR. Patients who were treated for PE between January 2016 to December 2021 were identified from the Clinical Data Analysis and Reporting System of the Hospital Authority of Hong Kong. Records on the electronic medical system were reviewed to identify patients who received catheter-based treatment with either AT or USCDT. Only patient who suffered from intermediate to high-risk PE were included in the

analysis. Both electronic and paper medical records of the index admission and subsequent outcomes of each patient were reviewed. This study was approved by the New Territories West Cluster Research Ethics Committee.

Patient risk stratification

PE risks stratification was performed based on 2019 European Society of Cardiology guideline for the diagnosis and management of acute PE [3]. High-risk PE was defined as patients with the presence of right ventricular dysfunction on either trans-thoracic echocardiogram or computed tomography of pulmonary arteries, and the presence of hemodynamic instability. Hemodynamic instability includes any one of the following clinical presentations: (1) cardiac arrest; (2) obstructive shock with systolic blood pressure less than 90 mmHg or use of vasopressors to achieve blood pressure greater than or equal to 90 mmHg despite adequate fluid status and presence of end organ hypoperfusion; or (3) persistent hypotension including systolic blood pressure less than 90 mmHg or a systolic blood pressure drop more than 40 mmHg for greater than 15 minutes not caused by new onset of arrhythmia, hypovolemia or sepsis. Intermediate-risk PE was defined by presence of right ventricle dysfunction on imaging but without the presence of hemodynamic instability. The pulmonary embolism severity index (PESI) score was calculated as well [3]. Absolute and relative contraindications for thrombolysis were defined as per the American Heart Association guideline on the use of systemic thrombolysis [12].

Procedures

Aspiration thrombectomy

AT was performed using Indigo CAT8 (Penumbra, Alameda, California, USA) with procedure as previously described [11]. Femoral venous access was used in all the cases, and the aspiration catheter was brought to the left or right pulmonary artery for thrombus aspiration with the aid of a separator. The end-point of the AT procedure is operator-dependent, with most operators stopping when significant recanalization in pulmonary arterial flow or improvement in hemodynamic was achieved. Systemic heparin was used in most of the cases. The dosage of heparin was adjusted in some cases with HBR at operator's discretion. After the procedure, both catheters and sheath were removed, and the femoral wound is compressed manually.

Ultrasound-assisted catheter-directed thrombolysis

USCDT was performed using the EkoSonic Endovascular System (Boston Scientific, Natick, MA, USA) with procedure as previously described [9]. Femoral venous access was used in all the cases, and the infusion catheters were brought to the targeted pulmonary artery. Two catheters were used for bilateral pulmonary artery embolism while one catheter was used in unilateral pulmonary embolism. Fixed dose of thrombolytic drugs was given via the drug lumen of the catheters by infusion at the rate of 1 mg/hour/catheter. The catheters were connected to a micro-sonic delivery system with the reusable EKOS Sonic control unit, which delivered 1.5 MHz–1.9 MHz low-power ultrasound to facilitate the infiltration of thrombolytics. The duration of USCDT varied but was generally continued for 12 hours. Afterwards, the whole system would be removed, and the femoral wound would be compressed manually.

Post-operative care

Patients were transferred back to the referring team after the intervention. Anticoagulation with systemic heparin was generally advised unless absolutely contraindicated. Choice of discharge anticoagulation was left to the individual physician's discretion.

End points

The primary end point was defined as 30-day PE related mortality. The secondary end point was defined as 30-day all-cause mortality. The primary safety endpoint was moderate to severe bleeding events. Bleeding events were defined according to the GUSTO classification [13]. GUSTO severe bleeding was defined as intracerebral haemorrhage or bleeding resulting in substantial hemodynamic compromise requiring treatment. GUSTO moderate bleeding was defined as bleeding requiring blood transfusion but not resulting in hemodynamic compromise. Quantification of packed cells given was defined as the number of units of red blood packed cells transfused within 72 hours post procedure. Difference in haemoglobin level was defined as change from initial haemoglobin level to the lowest haemoglobin level within 72 hours post procedure. If no post-procedure haemoglobin was checked, it was assumed the post-procedure haemoglobin level was the same as that before the procedure.

Statistical analysis

Patients were divided according to the intervention they received into AT and USCDT groups respectively. Descriptive characteristics were reported as number of cases and percentages or as mean \pm standard deviation. Chi-square test or Fisher's exact test were used to compare dichotomous covariates, and independent sample t test or Mann–Whitney U test were used to compare continuous covariates between the two groups. P value of <0.05 was considered statistically significant for all analyses. Analysis was performed using Statistical Package for the Social Sciences (SPSS), version 26.

Results

During the study period, a total of 28 patients with acute PE fulfilled the inclusion criteria. 14 of them received AT treatment, and 14 received USCDT treatment. Eight (28%) of the patients were high-risk, and 24 (85.7%) of them had contraindications to thrombolytics. The baseline characteristics of the two groups were summarized in [Table 1](#). There was no difference in the baseline characteristics between the two groups. Only alteplase was used in the USCDT group and the mean total dose was 19 mg.

There were 3 (10.7%) patients with PE related 30-day mortality and 5 with all-cause 30-day mortality. All mortality occurred in patients with high-risk PE treated with USCDT. These were summarized in [Table 2](#), and the details of each of the mortality case were summarized in [Table 3](#).

There were 10 (41.7%) patients with bleeding with 2 severe GUSTO bleeding and 8 moderate GUSTO bleeding. Most of the severe bleeding occurred in patients treated with USCDT, with 1 suffering from bleeding at the extracorporeal membrane oxygenation (ECMO) access site during the intervention procedure, and 1 suffering from a fatal intra-cranial haemorrhage (ICH) 10 days after the USCDT procedure. Most of the moderate bleeding were transfusion-related and were found mostly in the AT group within 72 hours of the index procedure. The procedural time was 107.6 ± 51 minutes in the AT group, and 57.1 ± 23 minutes in the USCDT group. The difference of procedural time was significant between groups ($p < 0.05$). These results were summarized in [Table 4](#).

Discussion

Our study reported the efficacy and safety of catheter-based treatment for patients with intermediate to high-risk PE and HBR. The PE-related mortality in our

Table 1. Characteristics of study population by treatment groups

	AT (n = 14)	USCDT (n = 14)	P value
Age	58.6 ± 19.6	58.1 ± 13.8	0.808
Male sex	6 (42.9)	8 (57.1)	0.450
Smoker	4 (28.6)	6 (42.9)	0.430
DM	2 (14.3)	3 (21.4)	1.000
HT	6 (42.9)	4 (28.6)	0.430
CVS	4 (28.6)	3 (21.4)	1.000
Malignancy	3 (21.4)	4 (28.6)	1.000
Recent surgery	3 (21.4)	2 (14.3)	1.000
ICH history	2 (14.3)	1 (7.1)	1.000
DVT (index)	10 (71.4)	5 (35.7)	0.058
C/I to lytic	14 (100)	10 (71.4)	0.800
Absolute	6 (42.9)	6 (42.9)	1.000
Relative	8 (57.1)	4 (28.6)	0.127
PE risk stratification			
High	6 (42.9)	2 (14.3)	0.209
Intermediate	8 (57.1)	12 (85.7)	0.430
PESI Score	135.1 ± 63.4	125.4 ± 56.4	0.667
PESI Class			0.144
Class 1	4 (28.6)	2 (14.3)	
Class 2	0 (0.0)	2 (14.3)	
Class 3	0 (0.0)	3 (21.4)	
Class 4	1 (7.1)	0 (0.0)	
Class 5	9 (64.3)	7 (50.0)	
Mechanical support	1 (7.1)	2 (14.3)	1.000
CPR before intervention	2 (14.3)	0 (0.0)	0.481
Bilateral PE	13 (92.9)	14 (100.0)	1.000

PE, pulmonary embolism; DM, Diabetes mellitus; HT, Hypertension; CVS, History of cardiovascular disease, including ischemic heart disease and ischemic stroke; VTE, Venous thromboembolism history; Malignancy, including history of malignancy or patient diagnosed to have malignancy in current admission workup; ICH history, History of intracranial hemorrhage. DVT (index), Deep vein thrombosis diagnosed in index admission; C/I to lytics, Contraindication to lytics; PESI score, Pulmonary Embolism Severity Index score; PESI Class, Pulmonary Embolism Severity Index Class; CPR before intervention, Cardio-pulmonary resuscitation before intervention. Values are presented as mean ± standard deviation or number (%).

Table 2. Clinical outcomes by AT and USCDT

	AT (n = 14)	USCDT (n = 14)	P value
PE-related mortality within 30 days	0 (0.0)	3 (21.4)	0.067
Mortality within 30 days	0 (0.0)	5 (35.7)	0.041

AT, Aspiration thrombectomy; PE, Pulmonary embolism; USCDT, Ultrasound-assisted catheter-directed thrombolysis.

study was 10.7%, which although was numerically higher than 7.8% as reported in the ICOPER registry [14], was similar to those in the high-risk group who received reperfusion therapy [4–8]. This reflects the significant hemodynamic instability in this group of patients and echoes the need for more rapid reperfusion therapy. USCDT works by the action of thrombolytics which takes time to break down the occlusive thrombus. The infusion time as set out in the pivotal randomized trial was 12 hours [9], which was similar to that employed in our group. Although the infusion time and the dosage might be shortened without compromising the efficacy [15], the reperfusion with USCDT was not instantaneous. On the contrary,

reperfusion is more rapid in catheter-based thrombectomy such as AT, as the procedure is guided by on-table hemodynamic as well as angiographic feedback. Therefore, in patients with high-risk PE who requires rapid reperfusion, catheter-based thrombectomy should be considered over USCDT.

In our study, the incidence of bleeding occurred in 41.7% of patients. Although this is much higher than the reported bleeding rate of 10% in patients receiving systemic thrombolysis [16], or 8% in patients undergoing surgical embolectomy [17], this reflects the high percentage (85.7%) of patients with HBR in our group. 2 severe GUSTO bleeding was reported and both were found in the USCDT group. In the pivotal randomized trial as well as the large prospective cohort study [9,10], patients with HBR were excluded from the USCDT arm. Thrombolytics as well as systemic heparin are required during the USCDT infusion, which will further increase the bleeding risk in these patients. Similar incidence of bleeding was reported with USCDT in patients with HBR [18]. AT on the other hands can be performed heparin-free and thus minimizing the risk of bleeding from anticoagulation or thrombolytics. In

Table 3. Mortality cases details

Patient	A	B	C	D	E
Age	49	56	87	61	76
Sex	Male	Male	Male	Female	Male
PE risk stratification	High	High	Intermediate	High	Intermediate
Contraindication to thrombolytics	Yes (Absolute)	No	No	Yes (Relative)	Yes (Absolute)
Total alteplase given	20 mg	20 mg	18 mg	4 mg ^a	24 mg
Mechanical circulatory support	Yes	Yes	No	No	No
Cause of death	Pulmonary embolism	Pulmonary embolism	Intra-cranial hemorrhage	Pulmonary Embolism	Sputum retention
Mortality day post operation	1	4	15	1	5

PE, pulmonary embolism.

Mortality day post operation: Day 0 defined as the day of operation.

^a The patient succumbed before completion of infusion of alteplase.

Table 4. Safety outcomes

	AT (n = 14)	USCDT (n = 14)	
Bleeding Incidence	7 (50%)	3 (21.4)	0.114
GUSTO severe	0 (0.0)	2 (14.3)	0.481
GUSTO moderate	7 (50.0)	1 (7.1)	0.033
Transfusion required within 72 hours	7 (50.0)	2 (14.3)	0.103
PC transfused (pints)	0.9 ± 1.2	0.6 ± 1.9	0.125
Drop in Hb (g/dL)	1.8 ± 2.1	1.6 ± 1.7	0.946
ICH	0 (0.0)	1 (7.1)	1.000
Procedural time (min)	107.6 ± 51	57.1 ± 23	0.004

ICH, Intra-cranial hemorrhage post-procedure; GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; Hb, Hemoglobin; PC, Pack cells; PE, Pulmonary embolism.

our study, although the total incidence of bleeding was higher in the AT group than the USCDT group, the bleeding was mostly transfusion-related and non-fatal. The higher transfusion-related bleeding in the AT group might be explained by the nature of the AT procedure, in which large quantities of blood was aspirated together with the emboli clots. The loss of blood might be ameliorated with the newer iteration of the device, which incorporates a sensor that will automatically stop aspiration if fresh blood is detected [19]. In patients with HBR, AT should therefore be considered if technically feasible as suggested by the American Heart Association [20].

Last but not the least, the procedural time of USCDT was significantly less than that of AT. This finding was similar to a study which compared large-bore aspiration thrombectomy versus catheter-directed thrombolysis [21,22] This might be explained by the difference in the nature of the procedure in which the USCDT only required placement of two catheters over bilateral main pulmonary arteries, while active manipulation of catheter and repeated aspiration might be required

during the AT procedure. The new aspiration catheter which has a larger lumen and higher suction force might speed up the procedure and offset the difference in procedure time.

There were several limitations in our study. Firstly, this was a retrospective cohort study with a small number of patients, which are prompted to bias. Secondly, no pre-specified protocol was used in triaging patients to either procedure, although no significant difference was identified in the baseline characteristics between patient groups. Thirdly, no procedure protocol was used to guide individual operators. This might lead to difference in procedure time and procedure outcomes. Last but not the least, only mortality data was available for primary endpoint analysis while some of the usual surrogate endpoints for evaluating the efficacy of reperfusion device in PE such as right ventricle/left ventricle ratio, right ventricular systolic pressure, or right ventricular systolic function were not available.

Conclusions

In this retrospective analysis of patients with intermediate to high-risk PE and HBR, catheter-based therapy was used. Among the two treatment modalities, AT was associated with lower rate of PE-related mortality in high-risk patients, a higher incidence of transfusion, and longer procedural time. Further study comparing these two treatment modalities with newer generation of devices should be considered to evaluate their efficacy and refine patient selection.

Ethical information

This study was approved by the New Territories West Cluster Research Ethics Committee of Hospital Authority in Hong Kong.

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None reported.

Conflict of interest

The authors have no conflict of interest to disclose.

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