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Early View

Research letter

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Thrombolysis for massive pulmonary embolisms in morbid obesity: a multi-site case control study

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Take home message: This case-control study assessed the efficacy and safety of systematic thrombolysis in morbidly obese patients with massive pulmonary embolisms. Thrombolysis at the conventional doses seems to have similar efficacy and bleeding rates in morbidly obese patients.

Massive or high-risk pulmonary embolism (PE) confers significant mortality risk, and systemic thrombolysis is widely accepted as the first-line treatment in patients without contraindications.[1] High-risk PE in patients with morbid obesity presents unique challenges concerning initial treatments and interventions; in particular, uncertainty over efficacy of weight-based dose adjustments and bleeding complications with antithrombotic therapy.[2] With increasing prevalence of obesity and its independent association with venous thromboembolism,[3] addressing challenges in management in this patient population has become increasingly relevant. This study evaluated the efficacy and safety of systemic thrombolysis given for massive PE in morbidly obese patients, compared to a matched cohort of patients with normal body mass index (BMI).

Patients with acute massive PE admitted to three hospitals in Queensland, Australia (Princess Alexandra Hospital, Logan City Hospital and Sunshine Coast University Hospital) over a 36 months period between June 2016 to June 2019 were screened. All patients who received systemic thrombolysis with a tissue plasminogen activator (tPA) on an intention-to-treat basis for confirmed massive PE on a computed tomographic pulmonary angiogram (CTPA) scan were included. Patients who underwent mechanical clot retrieval (either percutaneous or surgical embolectomy) or had catheter directed thrombolysis were excluded. Massive PE was defined as large clot burden PE with acute haemodynamic instability as characterised by cardiac arrest, obstructive shock or persistent hypotension (systolic blood pressure <90mmHg or systolic blood pressure drop ≥40mmHg lasting longer than 15 minutes and not caused by new-onset arrhythmia, hypovolaemia, or sepsis). The length of follow-up was 12 months.

Outcomes in patients with morbid obesity (weight >120 kg or BMI >40 kg/m^2) were compared to an age, gender and pulmonary embolism severity index (PESI) score matched cohort of non-obese patients. The primary outcome was the rate of all-cause 30-day mortality. Secondary outcomes included I) rate of major and clinically relevant non-major bleeding as defined by the International Society of Thrombosis and Haemostasis guidelines[4], II) length of hospital stay, III) rate of re-

presentation to hospital within 30-days, IV) rate of recurrent VTE at 6 months, and IV) all-cause mortality at 12 months following the PE.

Estimated frequencies and proportions for the variables were calculated in descriptive analysis. The non-parametric continuous variables were compared using the Mann-Whitney test. The relative risk and 95% confidence intervals (95% CI) were calculated for rates, and the differences were regarded as significant at p value <0.05. Ethical approval for this study was granted by the Queensland Metro South Human Research Ethics Committee (HREC/2019/QMS/57882).

A total of 15 morbidly obese patients received upfront systemic thrombolysis during the study period. Two morbidly obese patients who underwent catheter directed interventions without systemic thrombolysis were excluded. A total of 30 patients (n = 15 in morbidly obese group and n = 15 in matched control group) were included in the study with a median age of 59.7 years (IQR 42 to 73). The mean BMI in the 15 patients classified as morbidly obese was 42.7 kg/m^2 (SD 6.8). All patients had acute proximal bilateral PE resulting in right heart strain on diagnostic CTPA. Transthoracic echocardiograms on the day of admission to hospital in all patients showed evidence of right ventricular dysfunction and/or raised pulmonary artery systolic pressure. There was evidence of myocardial damage with elevated cardiac troponin in all patients. The PESI scores were either Class IV or V. Baseline clinical characteristics of the two study groups are summarised in Table 1.0.

Patients were treated with either Alteplase (loading dose of 10mg administered intravenously over two minutes followed by 90mg over two hours for all patients >65 Kg) or Telectaplase (a single bolus dose was administered intravenously over 5 seconds based on the patients' weight, with a maximum dose of 50mg), followed by intravenous heparin infusion for at least 24-hours. All patients were admitted to the intensive care unit for at least 24-hours following thrombolysis. A total of four patients (two in each group), received half-dose bolus of tPA at the discretion of the treating

physician. A minority (n=3, 10%) did not initially meet criteria for thrombolysis, however due to clinical deterioration in the first 24-hours of the admission, received systemic thrombolysis.

Table 1: Characteristics of study participants

Characteristics		Morbidly obese N = 15	Non-obese N = 15	P
Demographics				
Age / years (median/ IQR)		59 (42-73)	60 (37–75)	0.8
Gender female (n/ %)		7 (46.7)	7 (46.7)	-
Anthropometrics				
Height in cm (mean/ SD)		168.9 (9.8)	177.3 (5.9)	0.02
Weight in kg (mean/ SD)		129.7 (18.7)	86.9 (12.3)	0.002
BMI kg/m^2 (mean/ SD)		42.7 (6.8)	27.8 (3.3)	0.001
Pulmonary embolism				
Most proximal clot location	Saddle embolus (n/ %)	7 (46.7)	5 (33.3)	0.39
	Main PA (n/ %)	7 (46.7)	10 (66.7)	0.28
	Lobar arteries (n/ %)	1 (6.7)	0 (0)	-
Clot number	Bilateral	15 (100)	15 (100)	-
Right heart strain on CTPA (n/ %)		15 (100)	15 (100)	-
Clinical parameters				
Cardiac arrest (n/ %)		1 (6.7)	1 (6.7)	-
Syncope prior to presentation (n/ %)		8 (53.3)	7 (46.7)	0.68
First recorded SBP in mmHg (mean/ SD)		85 (18.8)	84 (24.9)	0.38
First recorded heart rate (mean/ SD)		110 (19.1)	108 (18.1)	0.71
SpO2 < 94% on presentation (n/ %)		12 (80.0)	11 (73.3)	0.86
PESI score	Class V – Very high risk	10 (66.7)	10 (66.7)	-
	Class IV – High risk	5 (33.3)	5 (33.3)	-
History of cardiac disease (n/ %)		1 (6.7)	2 (13.3)	0.68
History of pulmonary disease (n/ %)		3 (20.0)	1 (6.7)	0.61
History of active cancer (n/ %)		0 (0)	1 (6.7)	-
Echocardiographic parameters				
LV impairment (n/ %)		2 (13.3)	1 (6.7)	0.68
RV impairment	Severe	4 (26.7)	4 (26.7)	-
	Moderate	5 (33.3)	2 (13.3)	0.44
	Mild	8 (53.3)	3 (20.0)	0.22
RV dilatation	Severe	6 (40.0)	4 (26.7)	0.56
	Moderate	1 (6.7)	5 (33.3)	0.13
	Mild	7 (46.7)	5 (33.3)	0.48
RVSP in mmHg (mean/ SD) *		47 (12.9)	48 (10.1)	0.79
Laboratory markers				
Elevated troponin (n/ %)		15 (100)	15 (100)	-
Lactate on presentation (mean/ SD)		3.9 (2.7)	5.1 (3.1)	0.25
Thrombolysis				
Agent	Alteplase (n/ %)	14 (93.3)	12 (80.0)	0.43
	Tenecteplase (n/ %)	1 (6.7)	3 (20.0)	0.61
Half dose lysis (n/ %)		2 (13.3)	2 (13.3)	-
Rescue lysis due to deterioration (n/ %)		2 (13.3)	1 (6.7)	0.47
Anticoagulation on discharge				
Novel oral anticoagulant (n/ %)		9 (60.0)	8 (53.3)	0.79
Warfarin (n/ %)		6 (40.0)	6 (40.0)	-
Low molecular weight heparin (n/ %)		0 (0.0)	1 (6.7)	0.69
IQR = Interquartile range; SD = standard deviation; BMI = body mass index; PA = pulmonary artery; CTPA =				

computed tomography pulmonary angiogram; SBP = systolic blood pressure; SpO2 = oxygen saturation; PESI = pulmonary embolism severity index; LV = left ventricle; RV = right ventricle, RVSP = right ventricular systolic pressure. * in patients who had a sufficient tricuspid regurgitation velocity measurement.

The 30-day mortality rate was 13.3% (95% CI 0.0 - 32.8) in the obese group and 6.7% (95% CI 0.0 – 20.1) in the non-obese group (p=0.37). Major or clinically relevant non-major bleeding was seen in two (13.3%) obese patients (retroperitoneal and orbital bleeding) and four (26.7%) non-obese patients (gastrointestinal, retroperitoneal, intercoastal artery and abdominal wall haematoma). The length of hospital stay was higher in the obese group compared to non-obese group (median 11 days vs 7 days respectively, p=0.04). There was a trend towards an increased rate of re-presentations to hospital within 30-days in the obese group. The reasons for hospital re-presentations were chest pain (n=3), bleeding (n=1), new atrial fibrillation (n=1) and hospital acquired pneumonia (n=1) in the obese group and chest pain (n=1) in non-obese group. The rate of recurrent VTE at 6 months was low (n=0 in the obese group vs n=2 in the non-obese group). The all-cause mortality within 12 months was similar between the groups (n=3 (20.0%, 95%CI 6.3-45.9) in the obese group and n=2 (13.3%, 95%CI 2.5-39.1) in the non-obese group). Other than the patients who died, there was no lost to follow-up at six months, however one patient in each group were lost to follow-up at 12 months. Persistent right ventricular dysfunction on transthoracic echocardiography at six-months was seen in four (26.7%; 95%CI 10.5-52.4) morbidly obese and one (6.6%; 95%CI 0.0-29.8) non-obese patients. The mean right ventricular systolic pressure at six months was 29.3mmHg (SD 9.1) in the morbidly obese group compared to 24.5mmHg (SD 5.5) in non-obese group (p=0.069). None of the patients were diagnosed with chronic thromboembolic pulmonary hypertension (CTEPH) during the follow-up period.

This multicentre study found similar 30-day mortality risk for treatment of massive PE with systemic thrombolysis in morbidly obese patients and age, gender, and PE severity matched control. Mortality benefit from thrombolysis in massive PE may be inferred from historic trials,[5] although to our knowledge this study is the first study to report outcomes specific to morbidly obese patients. PE-

related mortality at 30-days was similar between our study and other real-world data in patients receiving thrombolysis for massive PE.[6] Rates of major bleeding were lower in our study perhaps due to changes in drug distribution in the morbidly obese patient group.[2] Our findings are also consistent with studies in thrombolysis for acute stroke, where obese patients have similar outcomes compared to non-obese patients.[7, 8]

A strength of this dataset is the high levels of diagnostic work-up including CTPA and echocardiograms substantiating the presence of large clot burdens and acute RV dysfunction. As well as this, treatment decisions were clinician-led within a real-world setting capable of mechanical and circulatory support, increasing the relevance of our findings to centres with PE-specific ICU management pathways. The longer duration of admission in obese patients may be attributed to obese patients receiving more cautionary care, especially given the potential for slower recovery and rehabilitation.

This study has several limitations. The small sample size in each treatment arm prevents the authors from making strong conclusions. The study did not have sufficient power to detect statistically significant differences in rates of bleeding. The clinical utility of half-dose thrombolysis in this patient population cannot be determined due to small patient numbers. Furthermore, the decision to administer systemic thrombolysis can vary between institutions, which may have caused selection bias and impact on the generalisability of our findings. Although none of the patients were diagnosed with CTEPH, routine investigations for chronic thromboembolic disease were at the discretion of individual clinicians and varied somewhat across the sites

In summary, despite the limitations, the present study shows new and interesting clinical outcome data on thrombolysis of massive PE in real-world morbidly obese patients. Our study provides much needed evidence in support of current thrombolysis protocols in morbidly obese patients with massive PE. Thrombolysis at the conventional doses seems to have similar efficacy and bleeding rates in morbidly obese compared to non-obese patients. The efficacy, safety and feasibility of

percutaneous catheter directed interventions compared to systemic thrombolysis therapy in morbidly obese patients with acute massive PE remains to be addressed. Larger randomised clinical trials comparing systemic thrombolysis and localised mechanical intervention are needed to determine the optimal treatment strategy for passive PE in this patient population.

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