Clinics in Surgery

Research Article
Published: 30 Apr, 2018

Exploring the Role of Sildenafil in Acute Pulmonary Embolism

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Abstract

Acute pulmonary embolism is a cause of significant morbidity and mortality. If thrombus burden is sufficient as to cause right ventricular strain, even "intermediate-high risk", normotensive patients have a 13% risk of death at 3 months. Current trials do not support thrombolysis in this group due to excess risk of bleeding. Novel strategies to support the haemodynamic response to acute PE may be advantageous.

We report our experiences of using Sildenafil in high or intermediate-high risk PE. 18 patients took Sildenafil 25 mg thrice daily for >3 months. A further patient received 12.5 mg thrice daily with dose reduction due to side effects. Despite markers of poor prognosis at presentation, all patients survived to 3 months. 7 received systemic thrombolysis, but none required invasive ventilation or advanced haemodynamic support. Now at median 9 months follow up, 2 cases of CTEPH have been confirmed. There have been no deaths directly attributable to thromboembolic disease.

Our findings demonstrate Sildenafil to be a safe, generally well-tolerated adjunct to standard treatment in this group. Larger controlled trials are now required to better ascertain the role of Sildenafil in this context.

Introduction

Acute Pulmonary Embolism (PE) is well recognized as a cause of significant morbidity and mortality. Features including Pulmonary Embolism Severity Index (PESI) score, markers of right ventricular strain and systemic hypotension are relied upon to identify patients at highest risk of adverse outcomes [1,2]. Systemic anticoagulation is the mainstay of treatment, with thrombolysis reserved for those with haemodynamic compromise ("high risk" PE) [1]. However even in the absence of systemic hypotension, the presence of Right Heart Strain (RHS) doubles the risk of mortality at 30 days (13% to 17%) and confers a higher risk of Chronic Thromboembolic Pulmonary Hypertension (CTEPH) [3-5].

Existing trials find that the benefits of thrombolysis in this "intermediate-high risk" group are offset by the increased risk of haemorrhage [6,7]. Catheter-directed thrombolysis strategies are under ongoing evaluation, but require access to specialist interventional facilities. Novel, readily available treatments that aim to alleviate RHS without increasing bleeding risk may therefore be advantageous.

Sildenafil is a widely available and well-tolerated pulmonary vasodilator, with an established role in primary Pulmonary Arterial Hypertension (PAH) and evidence of benefit in CTEPH [8-11]. Experimental models of acute PE have demonstrated Sildenafil to be effective in reducing both PVR and mean Pulmonary Artery Pressure (mPAP) [12-14]. This is further supported by case reports of Sildenafil administration improving haemodynamics in severely compromised patients with acute PE [15-17].

We report our experiences of using Sildenafil as an adjunct to standard therapy in 20 patients with either high or intermediate-high risk acute PE, the majority receiving 25 mg thrice daily for a minimum of three months. We review clinical features, evidence of RHS and outcomes both at presentation and at 3 months follow up.

Methods

Patients with high or intermediate-high risk PE were referred to the pulmonary hypertension team from our emergency department or admitting specialty team. Emergency care had typically been provided at the time of referral, including diagnostic imaging and initiation of anticoagulation

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Received Date: *15 Mar 2018*
Accepted Date: *27 Apr 2018*
Published Date: *30 Apr 2018*

Citation:
Hall H, Orton C, Mirza R, Shaw E, Ryan K, Madden BP. Exploring the Role of Sildenafil in Acute Pulmonary Embolism. Clin Surg. 2018; 3: 1963.

Table 1: Markers of right ventricular strain.

Echocardiographic features	Radiological features
RV:LV>0.9	
McConnell's sign*	
Raised PASP >30 mmHg	RV:LV>0.9-1.0
"60/60 sign" **	Interventricular Septal bowing
TR velocity >2.8 m/s	Reflux of contrast into IVC
PAAT <100 msec	
TAPSE <15 mm	

PASP: Pulmonary Artery Systolic Pressure; TR: Tricuspid Regurgitation; PAAT: Pulmonary Artery Acceleration Time; TAPSE: Tricuspid Annulus Plane Systolic Excursion; IVC: Inferior Vena Cava

*RV free wall hypokinesia with preserved apical motion; **RV ejection time <60 msec with PASP <60 mmHg

therapy.

All patients were assessed for clinical and radiological evidence of RHS. Salient features on 2D Transthoracic Echocardiography (TTE) or CT Pulmonary Angiogram (CTPA) are listed in Table 1. Cardiac biomarkers were measured, with Troponin T (TnT) >14 pg/ml and N Terminal pro-B type natriuretic protein (NT Pro-BNP) >600 pg/ml deemed significant in the absence of an alternative explanation.

Patients with evidence of RHS on TTE, CTPA or biochemistry, with or without systemic hypotension, were verbally consented to receive Sildenafil 25 mg tds in addition to usual care. Patients were monitored to discharge, and followed up with repeat TTE, CTPA and clinical evaluation at 3 months.

Results

Demographics

Between January 2015 and June 2017, 20 patients received at least one dose of Sildenafil. 45% (9/20) were male. Mean (± SD) age at presentation was 54 ± 16 years (range 19-78). Five had active malignancy, one had COPD, and two had known congestive cardiac failure. Initial investigations and follow-up TTE results for all patients are summarized in Table 2.

Initial presentation and management

All patients had clinically significant acute bilateral PE with a combination of clinical, radiological or biochemical markers of RHS. All had CTPA performed prior to referral. Bedside TTE was performed for 4 patients at presentation and performed in a further 15 patients at median day 1 of admission (range 0 - 6).

RHS was evident on TTE in 95% (19/20), on CTPA in 80% (16/20), with elevated cardiac biomarkers present in 94.7% (18/19). TnT and NT pro-BNP were measured in 95% (19/20) and 65% (13/20) respectively. TnT was raised in 94.7% (18/19), median 63 pg/ml (range 7-800). NT pro-BNP was raised in 76/9% (10/13), median 1505 pg/ml (84-10165).

Five patients had an estimated PASP >60 mmHg, suggestive of pre-existing Pulmonary Hypertension (PH); however all five had clinical and radiological features suggestive of large volume acute PE contributing significantly to this result. One patient (no. 13) self-discharged prior to undergoing TTE or TnT/NT Pro-BNP measurement, but re-presented and was started on Sildenafil after TTE and biomarker measurement during her second admission. A further patient (no. 10) deteriorated 48 hours post CTPA with presumed clot propagation and RHS on echo, but did not undergo repeat CT.

Seven patients received systemic thrombolysis with Alteplase; six were hypotensive at presentation and one deteriorated despite therapeutic heparinization. Two patients required oxygen delivery via high flow nasal cannulae. No patients experienced cardiac arrest and none required invasive ventilation or advanced haemodynamic support.

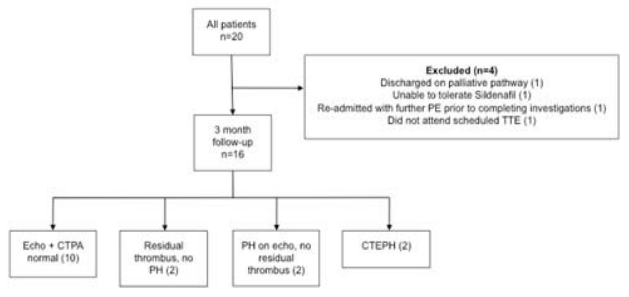

Figure 1: Patient outcomes.

All patients were discharged on systemic anticoagulation: low molecular weight heparin (Dalteparin, n=6), oral coumarins (Warfarin, n=5) or direct Xa inhibitors (Rivaroxaban, n=9). Choice was guided by concurrent comorbidities including malignancy, prior anticoagulation therapy and clinical response to initial agent. All patients were commenced on Sildenafil 25 mg thrice daily. One discontinued treatment after one dose due to side effects. The remaining 19 patients took Sildenafil for a minimum of three months.

Clinical follow up and outcomes

All initial 20 patients were alive at 3 months. After median 9 months (range 4-28) follow up, two deaths have occurred due to progressive malignancy, occurring after 10 and 18 months respectively. There have been no deaths directly attributable to thromboembolic disease.

Formal follow-up including CTPA, TTE and clinical assessment were completed for 16 patients. Two patients were omitted from ongoing follow up: one had significant neuro disability from underlying intracranial malignancy and was discharged under a palliative care pathway, and a second patient had discontinued Sildenafil after a single dose. Two additional patients failed to complete all intended investigations. Outcomes are summarized in Figure 1 and Table 2.

TTE was performed after 96 days (3-483), and CTPA after median 101 days (65-610). 62.5% (10/16) had no evidence of persistent RHS or residual thrombus. Of the remaining six patients, two have been diagnosed with CTEPH, two have PH evident on TTE but no residual thrombus burden, and two have persistent thrombi but without evidence of ongoing RHS. There was a trend towards higher rates of recovery in patients who underwent thrombolysis (80%, 4/5 vs. 54.5%, 6/11) but this was not statistically significant. 75% (3/4) of those with persistent PH, including both those diagnosed with CTEPH, had initial PASP >60 mmHg suggesting a degree of chronic PH existing prior to the acute presentation, for which additional investigations have been performed as indicated.

Adverse events

Two patients developed headaches with Sildenafil; one tolerated a reduced dose of 12.5 mg tds, the other discontinued treatment after the first dose. One stopped Sildenafil after 12 months treatment due to possible ocular complications, but subsequent ophthalmological review revealed no association. One patient stopped DOAC therapy

Table 2: Markers of right heart strain and clinical outcomes.

No.	Age/ gender	Raised TnT/NT pro-BNP	RHS on CTPA	Initial TTE	Follow-up TTE	Outcome
1*	68M	Yes	Yes	Bedside: dilated RV	Normal RV, no significant TR	Recovered
2	52F	Yes	Yes	Dilated RV, PASP 48-53 mmHg, TR velocity 3.09 m/2	PASP 40-45 mmHg, TR velocity 2.8 m/2	PH, no thrombus
3	77F	Yes	Yes	PASP 35-40 mmHg, TR velocity 2.9 m/s	Normal RV, no significant TR	Recovered
4	50F	Yes	Yes	Dilated RV, PASP 85-90 mmHg, TR velocity 4.1 m/s	Dilated RV, PASP 60-65 mmHg, TR velocity 3.6 m/s	CTEPH
5	52M	Yes	Yes	RV pressure overload, PASP 37 mmHg + RAP, PAAT 89 msec, TR velocity 3 m/s	Normal RV, PASP 25-30 mmHg, trivial TR	Residual thrombus
6	55M	Yes	Yes	Severe LV impairment, PASP 29 mmHg + RAP 15 mmHg	PAAT 110 msec, insufficient TR	Recovered
7*	59M	Yes	Yes	Bedside: dilated RV	NA	NA (palliated)
8	78F	Yes	Yes	PASP 35-40 mmHg, TR velocity 2.97 m/s	NA	NA (no echo)
9	68F	Yes	Yes	Dilated RV, PASP 55-60 mmHg, TR velocity 3.71 m/s	PASP 25 mmHg, TR velocity 2.49 m/s	Recovered
10*	19F	Yes	No**	Bedside: dilated RV	Normal RV, no significant TR	Recovered
11	63M	Yes	Yes	Dilated RV, PASP 75-80 mmHg, TR velocity 4.5 m/s	Normal RV, PASP 22-27 mmHg, TR velocity 2.34 m/s	Recovered
12*	35F	Yes	Yes	Dilated RV, PASP 63-68 mmHg, TR velocity 3.8 m/s	Normal RV, PASP 38-43 mmHg, TR velocity 2.9 m/s	PH, no thrombus
13	36F	Yes	Yes	Dilated RV, PASP 40-45 mmHg, TR velocity 3.3 m/s	PASP 27-32 mmHg, TR velocity 2.6 m/s	NA (stopped treatment)
14	66F	Yes	Yes	Dilated RV, PASP 70-75 mmHg, TR velocity 3.5 m/s	Overloaded RV, PASP 48-53 mmHg, TR velocity 3.49 m/se	CTEPH
15*	46M	Yes	Yes	Dilated RV, PASP 34-39 mmHg, TR velocity 3.7 m/s, positive McConnells sign	PASP 20-25 mmHg, TR velocity 2.3 m/s, PAAT 129 msec	Recovered
16*	56M	Yes	Yes	Bedside: dilated RV	Normal RV, PASP 25-30 mmHg, TR velocity 2.5 m/s	Recovered
17	40F	Yes	No	Normal RV, TAPSE 2 cm	Normal RV, no significant TR, TAPSE 2.3 cm	Recovered
18*	74M	Yes	Yes	Dilated RV, PASP >67 mmHg, TR velocity 3.6 m/s	PASP 32-37 mmHg, TR velocity 2.82 m/s	NA (no CTPA)
19	31F	No	Yes	Dilated RV, PASP 52-57 mmHg, TR velocity 3.61 m/s	PASP 22-27 mmmHg, trivial TR	Residual thrombus
20	53M	Yes	Yes	Dilated RV, PASP 48-53 mmHg, TR velocity 3.1 m/s	Normal RV, no significant TR, PAT 108 msec,	Recovered

*patients who received systemic thrombolysis; **Patient 10: CTPA performed 24 hours prior to clinical deterioration and echocardiogram.

prematurely post discharge and was re-admitted with new PE prior to completing routine follow-up.

Discussion

Sildenafil in acute PE

In acute severe PE, occlusion of the pulmonary vascular bed and release of vasoactive mediators (Thromboxane A2 and serotonin) contribute to a precipitous rise in pulmonary vascular resistance [12]. The healthy, thin-walled right ventricle is unable to overcome the sudden increase in after load. Acute RV dilation causes compression and impaired contractility of the Left Ventricle (LV) and this in addition to reduced LV filling causes a fall in cardiac output and haemodynamic decompensation [1]. There is therefore a rationale for treatments aiming to control the rise in PVR to support the deleterious effects on the right ventricle, in addition to standard anticoagulation or fibrinolysis.

Sildenafil is a widely used, orally available pulmonary vasodilator. It is a selective Phosphodiesterase-5 (PDE-5) inhibitor which potentiates the effects of cyclic Guanosine Monophosphate (cGMP), leading to rapid onset of pulmonary vasodilation within 15 min of administration. It is well established as a first line therapy for Class 1 pulmonary hypertension [8].

Sildenafil appears to be beneficial in established CTEPH, with small trials demonstrating improvement in PVR, WHO class and 6 min walk test distances [9-11].

In animal models of pulmonary hypertension provoked by acute PE, intravenous Sildenafil has been found to significantly improve PVR and mPAP without causing a fall in systemic Mean Arterial Pressure (MAP) [12-14].

Existing case reports have found administration of Sildenafil to substantially improve haemodynamics in patients in whom acute PE has caused severe compromise despite systemic or catheter-directed thrombolysis [15-17].

Significance and measurement of right ventricular strain

Even in "intermediate-high risk" patients, the presence of RHS is an independent risk factor for adverse outcomes. A 2014 met analysis by Cho *et al.* (n=3283) found a 37.3% prevalence of RV strain in hemodynamically stable patients with acute PE [4]. Those with RV strain had an increased short-term mortality rate of 13.7% vs. 6.5% (OR 2.29; 95% CI 1.61 to 3.26) [5].

Previous studies note the lack of consensus as regards reliable markers of RHS. The 2014 ESC guidelines find that commonly used parameters including TTE markers, CTPA and cardiac biomarkers have reasonably high sensitivity for RHS at 74% to 87% but lack specificity (35% to 54%) and the positive predictive value for any one measurement for mortality risk is low at 7% to 9% only. Some markers also need to be taken in context of the wider clinical picture. For example, a normal healthy right ventricle is unable to compensate against very severely elevated PA pressures. An estimated PASP >60 mmHg in the context of a normotensive patient with PE is therefore highly likely to suggest pre-existing pulmonary hypertension, and should not be interpreted in isolation as indicative of acute RHS.

Strengths and limitations of our data

We present a case series of patients with acute pulmonary embolus associated with RHS, in whom the addition of Sildenafil to standard treatments was well tolerated with few side effects. Outcomes were generally good with no thrombus-associated deaths seen after median 9 months. Use of Sildenafil in this setting has previously only been explored in animal studies and isolated case reports. Our findings should prompt larger, randomised trials to better establish the role of Sildenafil in this setting.

As with any uncontrolled case series, there are inherent limitations to the generalisability of these results. Reported cases are heterogeneous both in terms of pre-existing comorbidities, clinical severity and use of standard treatments including thrombolysis. Patients continued under care of the admitting team, and there is variation in the timing of conversion from parenteral to oral therapy, initial Sildenafil administration and choice of anticoagulant on discharge. Five patients had initial results suggesting a degree of pre-existing pulmonary hypertension, which may skew the interpretation of recovery rates seen at 3 months onwards. Similarly a significant number of patients received systemic thrombolysis which by design aims to rapidly improve the haemodynamic response to PE, though this cohort was too small to comment as to a difference in outcomes between the two groups.

Right ventricular strain was measured through indirect markers which, whilst widely relied upon in routine clinical practice, may lack the sensitivity and accuracy of data obtained invasively via right heart catheter. CTPA and TTE investigations were interpreted by on-call radiologists and echocardiogram technicians, and there may be differences in the interpretation of some of the more subtle markers of RHS. We recognise that the parameters used may lack specificity, and accordingly a proportion of patients may have rapidly recovered with anticoagulation alone. However the markers of RHS used are widely available to clinicians managing similar patients, and are reflective of current clinical practice and guidelines.

Conclusion

Sildenafil is a widely used pulmonary vasodilator. It is generally safe, widely available and well-tolerated. In this group of 20 patients with acute PE associated with RV strain, Sildenafil was used as an adjunct to standard anticoagulant therapy. Only one patient discontinued treatment due to side effects.

Although these patients had features at presentation that conferred increased risk of death, none required invasive ventilation or advanced haemodynamic support, and all survived to 3 months. Follow-up mortality rates remain low, with no deaths attributable directly to pulmonary embolism. Full recovery was observed in 62.5% at 3 months. CTEPH has been diagnosed in 2 patients (12.1%) after median 9 months follow up, though it is likely that both patients had some degree of pre-existing pulmonary hypertension.

Our experiences support the notion that Sildenafil can be used safely in this setting. Larger, randomised trials are now required in order to further elucidate the role of Sildenafil in acute pulmonary embolism.

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