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Safety and efficacy of fondaparinux as an adjunctive treatment to thrombolysis in patients with high and intermediate risk pulmonary embolism

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Abstract No data are available on the efficacy and safety of a combination of fondaparinux and thrombolysis in the setting of high to intermediate risk pulmonary embolism (PE). Patients submitted to thrombolysis and fondaparinux, presenting with ≥1 of the following criteria were included: (1) cardiogenic shock, (2) syncope, (3) ≥1 proximal thrombo-embolus at CT scan, (4) positive troponin test, (5) echocardiographic findings indicating right ventricular (RV) dysfunction. In-hospital results included death, recurrent PE, persistent RV dysfunction at 48 h echocardiography, bleeding complications. Twenty seven patients were included; 22 received a 2 h infusion of rt-PA and 5 received a 2 h infusion of streptokinase. Ten patients presented with cardiogenic shock (37%), 8 with syncope (30%), all had RV dysfunction. 82% of patients had an uneventful in-hospital course. One patient died during hospital stay from refractory shock. Thrombolysis failed in 2 patients (7%), requiring successful rescue surgical embolectomy. Bleeding events occurred in 2 patients (7%), of whom 1 required blood transfusion. Despite the small sample size, our data suggest that fondaparinux procures adequate tolerability compared to standard current therapy in combination with thrombolysis in high to intermediate risk PE.

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Background

Fondaparinux is a synthetic and selective inhibitor of factor Xa that has proven its efficacy and safety at different dose regimens as a preventive and curative treatment of thromboembolic disease when compared with heparins [1–3]. Its pharmacokinetic properties allow a simple, fixed-dose, once-daily regimen of subcutaneous injection without the need for monitoring. The use of pharmacological prophylaxis in patients undergoing major orthopedic surgery was suspected to entail potential increased risks of major bleeding, although this trend was not confirmed when higher curative dosing regimens were used in the treatment of DVT or low risk PE [1–3].

To date, the safety and efficacy of fondaparinux as adjunctive therapy to thrombolysis have never been assessed in the setting of high and intermediate risk acute PE, where UFH is currently the only recommended molecule [4]. However, data from studies conducted in ST elevation myocardial infarction (STEMI) patients receiving thrombolytic therapy demonstrated that 2.5 mg of fondaparinux given once daily significantly reduces mortality and reinfarction without increasing bleeding and strokes, when compared with UFH [5]. Whether these results can be extrapolated to patients suffering from high and intermediate risk pulmonary embolism is unknown, since the use of higher doses of fondaparinux as an adjunctive therapy to thrombolysis might be associated with an increased bleeding rate.

In this context, the aim of our study was to evaluate the safety and efficacy of a combination of fondaparinux and

thrombolysis in the setting of acute high and intermediate risk PE.

Materials and methods

Selection of patients

The study population was derived from a prospective, single-center registry of patients with confirmed pulmonary embolism.

Twenty seven patients with proven recent high and intermediate risk pulmonary embolism (symptom onset <15 days) were included in the registry between October 2006 and January 2008 if they met at least one of the following criteria: (1) cardiogenic shock defined as systolic blood pressure ≤90 mmHg, or a pressure drop of ≥40 mmHg, associated with clinical signs of organ hypoperfusion and hypoxia; (2) syncope; (3) one or more proximal thrombo-embolus at CT scan; (4) positive troponin test; or (4) at least one echocardiographic finding(s) indicating right ventricular dysfunction (RV/left ventricular end-diastolic diameter ratio ≥1 in the 4-chamber view, paradoxical septal systolic motion or pulmonary hypertension defined as a RV/atrial gradient >30 mmHg).

Patients with the following criteria were excluded: (1) contraindication to thrombolytic therapy; or (2) renal failure on admission, defined as creatinine clearance <30 ml/min.

The study protocol was approved by the local Ethics Committee and informed consent was obtained for all patients enrolled in the study.

Medication

Streptokinase or rt-PA could be used, according to the following regimens: (1) streptokinase was administered as a continuous intravenous infusion of 1.5 million IU over 2 h (started after an infusion of 40 mg of methylprednisolone); and (2) rt-PA was infused at a dose of 70 mg or 100 mg over 2 h, according to body weight (if body weight >70 kg, bolus of 10 mg followed by 90 mg over 2 h; if body weight <70 kg, bolus of 7 mg followed by 63 mg over 2 h). Both thrombolytics were only administered once fibrinogen level rose above 1 g/l.

Fondaparinux was given immediately at the beginning of thrombolytic infusion or before starting thrombolysis while waiting for the confirmation of the diagnosis. In heparin-pretreated patients referred for thrombolysis from other departments, fondaparinux was administered 12 h after the last injection of low molecular weight heparin. All patients received a single daily subcutaneous injection of 5.0 mg fondaparinux (if their body weight was <50 kg), 7.5 mg (if their body weight was 50 to 100 kg), or 10.0 mg (if their body weight was >100 kg).

Vitamin K antagonists (fluindione) were initiated when the patients were hemodynamically stable (48 to 72 h after thrombolytic infusion). Doses were adjusted to obtain an INR (International Normalised Ratio) target of 2.5 (range 2.0–3.0), for at least 6 months. Fondaparinux was stopped when the INR stayed between 2.0 and 3.0 for at least 2 consecutive days.

Clinical end points and in-hospital follow-up

Efficacy end point

The efficacy endpoint of in-hospital course was a combined endpoint including persistent clinical instability and residual echocardiographic right ventricular dysfunction within the first 36 h. Persistent clinical instability was prospectively defined as the presence of at least two of the following criteria: refractory cardiogenic shock; systemic arterial hypotension (defined as systolic blood pressure of ≤90 mmHg or a pressure drop of ≥40 mmHg for >15 min if not caused by new-onset arrhythmia, hypovolemia, or sepsis); severe hypoxemia (ie, room-air pulse oximetry of ≤90% or PaO_2 without oxygen therapy of ≤55 mmHg); or tachycardia (heart rate, ≥110 beats/min). Residual echocardiographic right ventricular dysfunction was defined as the persistence of at least two initial right ventricular dysfunction criteria.

Adverse events such as death, recurrent PE, repeat thrombolysis, surgical embolectomy and bleeding complications were noted throughout the hospital stay. Perfusion lung scans were performed within 6–8 days after onset of treatment. Perfusion impairment was graded as to the proportion of lung not perfused [6]. Patients with symptoms suggesting PE and with new perfusion defects on the lung scan or pulmonary angiogram were interpreted as having recurrent PE.

Safety end point

The safety end point included major and important bleeding complications.

Major bleeding complications were prospectively defined as any bleeding event that required blood transfusion, surgical control, discontinuation of thrombolytic or anticoagulant treatment; hemorrhagic stroke confirmed by computed tomography or autopsy; or any bleeding causing death or defined as a fall of 15% in hematocrit. Important bleedings, defined as a fall of 10% in hematocrit were also recorded [7]. Other bleeding events were considered as minor bleedings, and were not included in the safety end point.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation; categorical variables are expressed as percentage.

Results

Clinical presentation

The clinical characteristics of patients at hospital admission are reported in Table 1.

The study population comprised 11 men (40.7%) and 16 women (59.3%), mean age 68 ± 11 years (range 42–86). Twenty five proximal pulmonary embolisms were diagnosed with CT scan and one with ventilation-perfusion lung scintigraphy. One patient who presented in cardiogenic shock and with echocardiographic findings of severe RV overload received thrombolytic therapy before spiral CT scan examination.

Initial severity of PE

Ten patients (37.0%) presented with initial shock, 8 (29.6%) with syncope. The remaining 9 patients (33.3%) were hemodynamically stable, but presented initially with high troponin I (i.e., TnI >0.15 ng/ml) and BNP (i.e., BNP >200 pg/ml) levels.

All patients had echographic criteria of right ventricular dysfunction. Mean systolic pulmonary artery pressure was 56 ± 15 mmHg and all patients had a RV/atrial gradient >30 mmHg.

Table 1 Patient characteristics at diagnosis

	$N = 27$
Sex	
Male	11 (40.7%)
Female	16 (59.3%)
Age (years)	68 ± 11
History of thromboembolic disease	9 (33.3%)
Cardiopulmonary disease	3 (11.1%)
Hypertension	15 (55.5%)
Cancer	5 (18.5%)
Onset of symptoms	
≤5 days	12 (44.4%)
>5 days	15 (55.5%)
Syncope	8 (29.6%)
Heart rate ≥100 beats/min	14 (51.8%)
Cardiogenic shock	10 (37.0%)
ECG with RV overload	20 (74.1%)
DVT	17 (63.0%)
TnI >0.15 ng/ml	12 (44.4%)
BNP >200 pg/ml	17 (63.0%)
Thrombolytic agent	
Streptokinase	5 (18.5%)
rt-PA	22 (81.5%)

ECG: Electrocardiogram; RV: right ventricular; DVT: deep vein thrombosis; TnI: Troponin I; BNP: Brain Natriuretic Peptide

Table 2 In-hospital clinical outcome

	$N = 27$
Efficacy endpoint	3 (11.1%)
Death (recurrent PE)	1 (3.7%)
Persistent clinical instability	2 (7.4%)
Non-fatal recurrent PE	0
Bleeding endpoint	2 (7.4%)
Major bleeding	1 (3.7%)
Important bleeding	1 (3.7%)
Uneventful in-hospital course	22 (81.5%)

Treatment and in-hospital course

Twenty two patients (81.5%) received rt-PA and 5 (18.5%) streptokinase. Mean duration of fondaparinux administration was 8.6 ± 4.0 days. Table 2 describes in-hospital clinical outcome. Mean heart rate decreased by 21% (from 100 ± 22 to 79 ± 18 beats/min), while mean systolic blood pressure remained stable. Overall, the in-hospital clinical course was uneventful in 22 patients (81.5%).

Efficacy outcomes

Three patients (11.1%) met the clinical efficacy endpoint. An 86-year-old woman died from recurrent pulmonary embolism and refractory cardiogenic shock 3 h after admission. Two patients (7.4%) had hemodynamic instability associated with persistent echocardiographic findings of severe right ventricular dysfunction 24 h after fibrinolysis. Both patients underwent successful surgical embolectomy.

Among the 24 remaining clinically stable patients, 3 (11.1%) had residual echocardiographic right ventricular dysfunction as previously defined (persistence of at least two initial right ventricular dysfunction criteria) (Table 3).

Safety outcomes

There was 1 major bleeding, and 1 important bleeding (total 2 events, 7.4%). The major bleeding complication occurred at the surgical site of a 71-year-old man who had undergone elective hip replacement two weeks previously. Management of bleeding in this patient required blood transfusion. Fondaparinux was replaced by UFH in

Table 3 In-hospital echocardiographic outcome

Echocardiographic findings	Pre-thrombolysis ($N = 27$)	Post-thrombolysis ($N = 26$)
RVEDD/LVEDD ratio ≥1	18 (66.7%)	4 (15.4%)
Spap >30 mmHg	27 (100%)	20 (76.9%)
Intracardiac thrombus	3 (11.1%)	0
Paradoxical septal motion	17 (63.0%)	4 (15.4%)
At least 2 of the above	22 (81.5%)	5 (19.2%)

RVEDD = Right ventricular end-diastolic diameter; LVEDD = Left ventricular end-diastolic diameter; sPAP = systolic pulmonary artery pressure

order that anticoagulant treatment could be neutralized if recurrent bleeding occurred. Infusion of recombinant coagulation factor VIIa and surgery were not required. A 57-year-old man with cirrhosis experienced an important bleeding complication without any identifiable bleeding site. Fondaparinux was not stopped. Clinical evolution of these 2 patients was favorable.

Discussion

Fondaparinux is a synthetic and selective inhibitor of factor Xa that has proven its efficacy and safety as a preventive and curative treatment of thromboembolic disease. The predictable and sustained anticoagulant effect of this drug for 24 h allows once-daily injection, and since it does not cross-react with heparin-induced antibodies, platelet count monitoring is no longer needed.

Our study is the first study to report the immediate clinical course of acute pulmonary embolism patients who received fondaparinux as adjunctive therapy to thrombolysis in the setting of acute high and intermediate risk pulmonary embolism.

Efficacy end point

Three patients (11.1%) met the clinical efficacy endpoint criteria, of whom one patient died from refractory shock and two patients required successful surgical embolectomy for persistent clinical instability. This confirms our previous findings reporting 8.2% of failed thrombolysis in UFH treated patients [8]. Moreover, the mortality rate was 4.3% in PE patients treated with thrombolysis and UFH in a recently published meta-analysis [9]. Fondaparinux thus seems to have similar in-hospital efficacy to UFH in the setting of PE submitted to thrombolysis, confirming results observed in the setting of stable thrombo-embolic disease [1, 2]. Additionally, this corroborates data on the efficacy of a fondaparinux-thombolysis association observed in the initial treatment of STEMI [5].

Safety end point

Two bleeding complications (7.4%) occurred during in-hospital course, including one important bleeding (3.7%) without any identifiable bleeding site and one major bleeding (3.7%) at the surgical site of an elective hip replacement. In a previous meta-analysis, fondaparinux 2.5 mg once daily was associated with a trend towards an increase in the incidence of major bleeding complications in patients undergoing orthopedic surgery [3]. However, in the initial treatment of hemodynamically stable patients with DVT and PE, fondaparinux 5–10 mg was associated with low rates of major bleedings (1.1% and 1.3%, respectively) [1, 2]. In the meta-analysis by Wan [9], major bleedings occurred in 9.1% of patients treated with thrombolysis and UFH, whereas in MAPPET-3, major bleedings occurred in 0.8% of patients submitted to thrombolysis [10]. Although the small sample size of this study does not make it possible to draw any definitive conclusions, the combination of fondaparinux and thrombolysis does not seem to be associated with an increase in bleeding events compared with UFH.

Limitations

This study is not a prospective randomized controlled trial and should be considered as pilot study derived from a single-center registry. As in most registries, neither diagnostic work-ups nor therapy were controlled. Moreover, our study is clearly under-powered, and no definitive conclusions can be drawn on the basis of these results.

Conclusion

Although the sample size of this pilot study is too small to firmly establish the safety and efficacy of fondaparinux as an adjunctive therapy to thrombolysis in the setting of massive and submassive acute PE, our results indicate that fondaparinux procures adequate tolerability compared to standard current therapy in this indication.

A randomized trial is warranted before administration of a combination of thrombolysis and fondaparinux in routine clinical practice can be advocated in this setting.

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