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Full Length Article

Safety, feasibility and patient reported outcome measures of outpatient treatment of pulmonary embolism

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ABSTRACT

Background: Despite growing evidence on safe and feasible outpatient treatment for acute pulmonary embolism (PE), the majority of patients is still treated in an inpatient setting. This is probably due to a lack of clear guidelines on this subject.
Objectives: To evaluate safety and patient reported outcome measures (PROM) on outpatient treatment of acute PE.
Methods: We conducted a prospective cohort study. 250 patients presenting with acute PE and Pulmonary Embolism Severity Index (PESI) class I or II were enrolled. Safety of outpatient treatment was assessed by measuring all-cause mortality, recurrent venous thromboembolism (VTE) and episodes of relevant bleeding, with a follow-up period of four weeks and six months. Additionally, PROM's on outpatient treatment were evaluated by repeatedly measuring VAS-scores for pain and dyspnea during the recovery, and by assessing the improvement in SF-36 scores between admission and after six months.
Results: We found an all-cause mortality rate of 0.4% (95% CI 0.07–2.23), rate of recurrent VTE of 0% (95% CI 0–1.51) and rate of relevant bleeding episodes of 6.4% (95% CI 3.98–10.14). VAS-scores improved significantly during the first 24-h after admission, and continued to improve significantly after five days of home treatment. SF-36 scores on 6 out of 8 domains improved significantly between admission and after six months.
Conclusions: Our study shows that outpatient treatment is safe in selected low-risk patients based on their PESI score. Additionally, our data on patient reported outcome measures support the presumption of a good course of recovery during outpatient treatment.

1. Introduction

Pulmonary embolism (PE) and deep venous thrombosis (DVT) are considered conditions within the same spectrum, sharing the same etiology. Every year, approximately 3500 people suffer from PE in The Netherlands [1]. Clinical presentation and clinical course are very variable, ranging from only mild discomfort to occasional cardiogenic shock and death.

Therapy of acute PE consists of low-molecular-weight heparin (LMWH), fondaparinux, vitamin K antagonists (VKA's), or direct oral coagulants (DOAC's). The major complication of this anticoagulant therapy is an episode of major bleeding. However, during non-optimal anticoagulant state there is a risk of recurrent venous thromboembolism (VTE). Traditionally, all patients presenting with acute PE are treated in an in-patient manner where they can be closely monitored for these adverse events. However, previous studies have shown that the risk of these adverse events remains present after a mean 6-day period of hospitalization [2]. Additionally, standard care for DVT has been in an outpatient setting for years, while treatment for DVT and PE are essentially the same [3]. Furthermore, about one third of all patients with DVT appear to have asymptomatic PE as well [4–5]. However, they are not routinely tested for PE and as a consequence this group is already being treated safely as outpatients. This raises the question whether in-patient treatment of acute PE is necessary in all cases, or if part of these patients might be safely treated as outpatients. Over the past years evidence on the possibility of safe and feasible outpatient treatment of acute PE has been accumulating. Several risk stratification tools have been suggested for selecting patients who are of low risk for adverse events, of these the Pulmonary Embolism Severity Index (PESI) is the most extensively validated [6–9]. However, evidence on the use of the PESI as a tool for selecting patients suitable for outpatient treatment is not abundant; only one RCT has been conducted [10]. A

Abbreviations: PE, pulmonary embolism; PROM, Patient Reported Outcome Measure; PESI, Pulmonary Embolism Severity Index; VTE, venous thromboembolism; VAS-score, visual analogue scale score; SF-36, short form health survey (36); DVT, deep venous thrombosis; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist; INR, international normalized ratio; 95%CI, 95% confidence interval.

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recent Cochrane review therefore graded the evidence as low quality, stating that further research is required before informed practice decisions can be made [11]. Our study aims to contribute to previously conducted studies on the safety of outpatient treatment by providing data on all-cause mortality, recurrent VTE and relevant bleeds with a follow-up period of 6 months, whereas previous studies have employed follow-up periods with a maximum of 3 months. Additionally, we will evaluate patient reported outcome measures of outpatient treatment by monitoring the course of recovery and improvement in quality of life during and following outpatient treatment.

2. Methods

Our study is a prospective cohort study conducted at Isala, Zwolle, the largest non-academic teaching hospital in the Netherlands (776 clinical beds). Approval of the local ethics committee was received. All patients presenting with acute PE between 1 July 2008 and 30 June 2013 were classified according to the PESI criteria. Diagnosis had to be verified with a spiral CT-scan or ventilation-to-perfusion scan, or diagnosis was based on clinical suspicion combined with a diagnosis of a new proximal DVT on ultrasound. Patients classified as "very low risk" or "low risk" (PESI class I or II) were included in the study. Exclusion criteria were hospital admission longer than 24 h prior to the PE, use of anticoagulants prior to the PE, place of residence >30 km from the hospital, inability to fill in the queries (e.g. due to dementia or analphabetism), and pregnancy. Data on excluded patients were not registered. Included patients were admitted to the hospital for <24 h prior to discharge. During the short admission patients received their first dose of tinzaparin (low-molecular-weight heparin (LMWH)) and simultaneously, treatment with acenocoumarol (vitamin K antagonist (VKA)) was initiated. In the first five days of outpatient treatment, a home-nurse came by the patient's residence daily. They checked on the patient's condition and recovery, and managed the daily treatment with LMWH for a minimum of five days, or until an adequate INR (within a range of 2.0–3.0 for two consecutive days) was reached. The LMWH was administered preferably by the patient himself, or otherwise by the nurse. Anticoagulant therapy by measuring INR was controlled by the Dutch Thrombosis Services, an institute that organizes out-of-hospital treatment with VKA's in the Netherlands by measuring INR values and dose adjustments. After four weeks a visit to the attending physician was scheduled. After six months the patients had their last consult with their physician. At this point in time it was decided whether anticoagulant treatment could be stopped or should be continued.

2.1. Measurement instruments

The Visual Analogue Scale (VAS) is a validated tool for the quantification of perception of pain [12–13], however, it has not been validated for the same use in dyspnea. Nonetheless, lacking a validated tool to measure patient's perception of dyspnea, we have used the VAS-score for this purpose as well. VAS-scores were obtained by letting patients mark their perception of the pain and dyspnea on a continuous line between two end-points. These marks were converted to a number from 0 to 10 (rounded to one decimal place) by the research team. The Short Form (36) Health Survey (SF-36) is a patient-reported questionnaire, used to measure health status in patients with chronic illness. It measures health status over 8 distinct domains. We have used a validated Dutch version of this questionnaire to assess the improvement in the patient's quality of life between the onset of the symptoms and after 6 months of treatment [14].

2.2. Data collection

Patient characteristics were obtained during the short hospital admission by filling in a standard form. VAS-scores were measured at 7 moments during the treatment: on admission, at discharge, during the first 5 days of outpatient treatment, at day 30 and at 6 months. Patients filled in an SF-36 query twice; on admission and during the final consult after 6 months. At this final consult was also inventoried if any adverse events occurred.

2.3. Outcome measures

The primary outcomes were all-cause mortality, recurrent VTE and relevant bleeding after 4 weeks and 6 months. Relevant bleeding was defined as any bleeding described by the patient as severe. Recurrent VTE was defined as recurrent PE, or new or recurrent DVT. Diagnostic criteria for recurrent PE were a new intraluminal filling defect on spiral CT, a new perfusion defect involving 75% or more of a lung segment with corresponding normal ventilation on a ventilation-perfusion scan, or confirmation of a new PE on autopsy. Diagnostic criteria for (recurrent) DVT were non-compressibility of a venous segment on ultrasonography, or a substantial increase (≥4 mm) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography.

Secondary outcomes were course of recovery measured as VAS-scores for pain and dyspnea during 6 months of treatment, and improvement in quality of life measured as an improvement in SF-36 scores between admission and after 6 months of treatment.

Table 1
Patient characteristics.

Age ($n = 250$)		53.2 ± 15.1
Gender ($n = 250$)	Male	119 (47.6%)
	Female	131 (52.4%)
Smoking status	Current smoker ($n = 245$)	42 (17.1%)
	Ex-smoker ($n = 202$)	92 (45.5%)
	Pack years ($n = 122$)	11.0 (4.0–25.0)
Weight ($n = 244$)		87.2 ± 17.9
BP systolic ($n = 243$)		138.1 ± 17.3
Pulse ($n = 243$)		82.3 ± 15.4
O2-oxygenation ($n = 244$)		97.0 (95.0–98.0)
Hormonal contraceptive[a] ($n = 129$)		46 (35.7%)
Wells score ($n = 247$)	PE unlikely (≤4)	146 (59.1%)
	PE likely (>4)	101 (40.9%)
D-dimer ($n = 190$)	<0.5	1 (0.5%)
	≥0.5	189 (99.5%)
Diagnosis ($n = 250$)	CT-scan	235 (94.0%)
	V/Q-scan	10 (4.0%)
	DVT on echo duplex	5 (2.0%)
Isolated subsegmental PE ($N = 235$)		37 (16%)
Associated DVT at diagnosis ($N = 250$)		75 (30%)
PESI score ($n = 250$)	Total	59.3 ± 16.4
	Age	53.2 ± 15.1
	Male	119 (47.6%)
	Cancer	4 (1.6%)
	Heart failure	1 (0.4%)
	Chronic lung condition	8 (3.2%)
	Pulse ≥ 100 b.p.m.	12 (4.8%)
	Systolic BP < 100 mm Hg	1 (0.4%)
	Respiratory rate ≥ 30/min	1 (0.4%)
	Temperature < 36 °C	0 (0%)
	Altered mental status	0 (0%)
	Oxygen saturation < 90%	2 (0.8%)
PESI class ($n = 250$)	I	145 (58.0%)
	II	100 (40.0%)
	III	5 (2.0%)
Admission period ($n = 250$)	1 day	221 (88.4%)
	2 days	25 (10.0%)
	3 days	4 (1.6%)

Displayed as n (%), mean ± SD or median (1st–3rd quartile).
[a] female patients.