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Outpatient treatment of symptomatic pulmonary embolism: A systematic review and meta-analysis☆

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ABSTRACT

Background: Patients with acute deep vein thrombus (DVT) can safely be treated as outpatients. However the role of outpatient treatment in patients diagnosed with a pulmonary embolism (PE) is controversial. We sought to determine the safety of outpatient management of patients with acute symptomatic PE.

Materials and Methods: A systematic literature search strategy was conducted using MEDLINE, EMBASE, the Cochrane Register of Controlled Trials and all EBM Reviews. Pooled proportions for the different outcomes were calculated.

Results: A total of 1258 patients were included in the systematic review. The rate of recurrent venous thromboembolism (VTE) in patients with PE managed as outpatients was 1.47% (95% CI: 0.47 to 3.0%; I^2: 65.4%) during the 3 month follow-up period. The rate of fatal PE was 0.47% (95% CI: 0.16 to 1.0%; I^2: 0%). The rates of major bleeding and fatal intracranial hemorrhage were 0.81% (95% CI: 0.37 to 1.42%; I^2: 0%) and 0.29% (95% CI: 0.06 to 0.68%; I^2: 0%), respectively. The overall 3 month mortality rate was 1.58% (95% CI: 0.71 to 2.80%; I^2: 45%). The event rates were similar if employing risk stratification models versus using clinical gestalt to select appropriate patients for outpatient management.

Conclusions: Independent of the risk stratification methods used, the rate of adverse events associated with outpatient PE treatment seems low. Based on our systematic review and pooled meta-analysis, low-risk patients with acute PE can safely be treated as outpatients if home circumstances are adequate.

Introduction

Patients with acute deep vein thrombus (DVT) can safely be treated as outpatients [1–4]. Outpatient treatment of DVT is recommended with grade 1B evidence in the most recent American College of Chest Physicians (ACCP) guidelines [5]. However the ACCP guidelines and other scientific societies have not firmly recommended outpatient therapy for patients with low-risk acute pulmonary embolism (PE) [5,6]. Clinicians appear reluctant to discharge PE patients due to a perceived lack of high quality data regarding both appropriate patient selection and outcomes with home treatment [7].

Several studies have reported that outpatient management or early discharge of patients with acute PE is safe and effective [8–13]. Two systematic reviews suggested that patients with acute PE treated as outpatients had low incidences of major bleeding, recurrent venous thromboembolism (VTE), and mortality [14,15]. However the quality of the included studies was low and subsequent and recent larger observational studies and randomized control trials were not included [8,11,16,17]. More recently, two additional systematic reviews of the outpatient management of acute symptomatic PE were published [18,19]. However the first review did not include studies of patients with acute PE managed with early discharge and did not perform a meta-analysis [18]. The last review included both retrospective and prospective studies which lower the overall quality of evidence from which the event rates are derived [7,19].

In this systematic review and meta-analysis we sought to determine the feasibility and safety of outpatient treatment (including early discharge). Furthermore, we attempted to compare the outcome event rates when risk stratification models are applied versus using clinical gestalt to select appropriate patients for outpatient

Abbreviations: ACCP, American College of Chest Physicians; CI, Confidence Interval; CTPA, CT Pulmonary Angiogram; DVT, Deep vein thrombus; EBM, Evidence Based Medicine; ICH, Intracranial Hemorrhage; LMWH, Low Molecular Weight Heparin; NT-proBNP, N-terminal Pro-hormone of Brain Natriuretic Peptide; PE, Pulmonary Embolism; PESI, Pulmonary Embolism Severity Index; RCTs, Randomized Controlled Trials; UFH, Unfractionated Heparin; VTE, Venous Thromboembolism; V/Q, Ventilation-perfusion.

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management. Finally, short-term (<14 days) outcome event rates were evaluated.

Materials and Methods

Search Strategy

We conducted a systematic literature search to identify potential studies on MEDLINE (1950 to week 4 of June 2012), EMBASE (1980 to end of June 2012), the Cochrane Central Register of Controlled Trials, and all evidence-based medicine reviews (e-Table 1 – online). We also sought publications through a hand-search of potentially relevant journals and International Society of Thrombosis and Haemostasis conference proceedings (2003-2011). We also reviewed the references of included studies and previous systematic reviews for additional potential studies. There were no restrictions on language or publication year.

Study Selection

Two investigators (S.P. and M.C.) independently screened the titles and abstracts of articles to find potentially relevant articles. Two investigators (S.P. and M.C.) then reviewed potentially relevant articles in full length to ensure that they satisfied these criteria: 1) Prospective enrollment of patients with objectively confirmed symptomatic PE. Pulmonary embolism was diagnosed with a high-probability ventilation-perfusion (V/Q) lung scan or a segmental or larger pulmonary artery filling defect on either computed tomography (CTPA) or pulmonary angiography; 2) patients received treatment for a minimum of 3 months with anticoagulation therapy (vitamin K antagonist, weight-based or adjusted-dose unfractionated heparin, weight-based or fixed dose low molecular weight heparin (LMWH)); 3) all outcomes categories were reported including VTE recurrence, major bleeding, fatal PE, fatal intracranial hemorrhage (ICH). We included randomized controlled trials and prospective cohort studies. We excluded review articles, case reports, letter to editor, editorials, retrospective, and unrelated studies. The clinical course of patients with suspected pulmonary embolism. Moreover, we did not include studies if outcome data was not separately reported (or was unavailable) for patients with PE. Appendix Fig. 1 (online) details the Study Selection Flow chart.

Outcome Measures

Recurrent VTE (recurrent PE and DVT) was defined as a new segmental mismatch on V/Q scan, a new intra-luminal filling defect on CTPA or pulmonary angiography, or a new non-compressible segment on deep leg vein. The rate of recurrent VTE used to determine the safety of outpatient treatment of acute PE was ≤3% during a 3-month follow-up period [20,21]. Major bleeding was defined as bleeding that required transfusion of 2 or more units of packed red blood cells or caused a fall in hemoglobin of 20 g/L or more, involved a critical site (e.g. intracranial), or was fatal [22] or as defined by the investigators of the individual studies.

Quality Assessment

We assessed the methodological quality of the included studies using the Risk of Bias Assessment Tool from the Cochrane Handbook for randomized trials [23] and the Newcastle-Ottawa Quality Assessment scale for observational studies [24].

Data Synthesis and Statistical Analysis

Ninety-five percent confidence intervals (95% CI) were calculated for each rate using the averaged, inverse variance-weighted estimates from each study. We calculated the pooled proportions, via random effects model, for the different outcomes at 3-months of follow-up (Stats Direct software, version 2.7.9). Pooled proportion meta-analysis was also performed for short-term outcomes for up to 14 days of follow-up. Sensitivity analyses (RCTs vs. cohort studies; outpatients vs. early discharge) were conducted to explore heterogeneity. The I^2 statistic was used to estimate total variation among the pooled proportions. An I^2 value <25% was considered low level of heterogeneity; 25-50% was moderate, and >50% was considered high level [25].

Results

We identified 1564 citations in our literature search and 16 articles were found to be potentially eligible (Appendix Fig. 1 – online). Five of these articles were then excluded. Three articles because the outcome measures were not reported specifically for patients with acute PE [26–28] and two because patients had not been managed as outpatients [29,30]. The remaining 11 studies were included in our systematic review. Eight were prospective cohort studies [8,11–13,31–34] and 3 were randomized controlled trials (RCT's) [16,17,35]. Furthermore, 2 studies did not report outcomes at 3 months and could not be used in our pooled meta-analysis [12,13].

Table 1 shows the baseline characteristics of the included studies. A total of 1258 patients were included in the systematic review. Eight of the studies exclusively included patients that were treated entirely as outpatients. Two studies included patients that were discharged early [16,32] and 1 study reported early discharge and outpatient groups separately [34]. Early discharge was generally defined as inpatient stay of 1-3 days [16,32]. Most studies treated patients with intravenous unfractionated heparin or subcutaneous LMWH in combination with a vitamin K antagonist.

Outcome events in the individual studies and the pooled event rates during the 3 months of follow-up are reported in Tables 1 and 2, respectively. The rate of recurrent VTE in patients with PE managed as outpatients was 1.47% (95% CI: 0.47 to 3.0%; I^2: 65.4%) during the 3 months follow-up period. The pooled rate of fatal PE was 0.47% (95% CI: 0.16 to 1.0%; I^2: 0%). The rates of major bleeding and fatal ICH were 0.81% (95% CI: 0.37 to 1.42%; I^2: 0% and 0.29% (95%CI: 0.06% to 0.68%; I^2: 0%), respectively. The overall mortality rate was 1.58% (95% CI: 0.71 to 2.80%; I^2: 45%). Sensitivity analyses assessing event rates according to study design (cohort vs. RCT) or type of management (outpatients vs. early discharge) did not significantly alter heterogeneity of pooled estimates (data not shown).

Five of the 11 studies used risk stratification models to select patients for outpatient treatment and the remainder used clinical gestalt (i.e. general impression that PE patient can be treated with outpatient therapy). The studies that used clinical gestalt utilized specific exclusion criteria to select low-risk patients for outpatient management. (e-Table 2- online). The pooled rates of VTE recurrence for the clinical gestalt subgroup versus the risk stratification subgroup were 1.88% (95% CI: 0.11% to 5.73%; I^2: 74.4%) and 1.4% (95% CI: 0.4% to 2.9%; I^2: 45%), respectively. Similarly, the pooled rate of major bleeding for patients stratified using clinical gestalt was 0.62% (95% CI: 0.059% to 1.79%; I^2: 14.7%) compared to 0.94% (95% CI: 0.4% to 1.8%; I^2: 25%) for patients identified using a risk stratification model.

Short term outcomes were reported in 5 studies for follow up period of <14 days (Table 3). A total of 552 patients were included in these subgroup analyses. Pooled event rates for <14 days of follow-up are reported in Table 4. The pooled rate of VTE recurrence was 0.28% (95% CI: 0.013% to 0.89%; I^2: 0%) during the short-term follow-up period. The short term pooled risk of major bleeding was 0.46% (95% CI: 0.022% to 1.46%; I^2: 30%). The pooled overall mortality rate was 0.41% (95% CI: 0.006% to 1.46%; I^2: 44%).

The quality of the included studies is depicted in e-Tables 3 and 4 (on-line only). Two out of the 3 RCTs reported adequate sequence generation and allocation concealment (e- Table 3) [23]. Patients and physicians were blinded in one study [35]. All 3 trials addressed incomplete outcome data and were free of selective outcome reporting. All