A meta-analysis of bed rest versus early ambulation in the management of pulmonary embolism, deep vein thrombosis, or both☆

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Abstract

Background: Bed rest is often recommended as part of the management of deep vein thrombosis (DVT) and pulmonary embolism (PE), though this recommendation is not clearly evidence-based.

Methods: Using the Cochrane Central Register of Controlled Trials, Medline, and Embase, this meta-analysis considered all randomized studies and prospective registries that compared the outcomes of patients with DVT, PE, or both, managed with bed rest versus early ambulation, in addition to anticoagulation. For each study, data regarding the incidence of new PE, new or progression of DVT, and death from all causes, were used to calculate relative risks (RR) and 95% confidence intervals (CI).

Results: The 5 studies retained in this analysis included a total of 3048 patients. When compared to bed rest, early ambulation was not associated with a higher incidence of a new PE (RR 1.03; 95% CI 0.65–1.63; p=0.90). Furthermore, early ambulation was associated with a trend toward a lower incidence of new PE and new or progression of DVT than bed rest (RR 0.79; 95% CI 0.55–1.14; p=0.21) and lower incidence of new PE and overall mortality (RR 0.79; 95% CI 0.40–1.56; p=0.50).

Conclusions: Compared with bed rest, early ambulation of patients with DVT, PE or both, was not associated with a higher risk of progression of DVT, new PE or death. This meta-analysis does not support the systematic recommendation of bed rest as part of the early management of patients presenting with DVT, PE of both.

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The management of patients with acute deep vein thrombosis (DVT), pulmonary embolism (PE), or both, remains controversial. Over 50 years ago, unfractionated heparin was found to lower the risk of PE [1]. Confinement to bed rest was mandatory, since heparin was administered as a continuous intravenous infusion. The efficacy of low-molecular-weight heparin (LMWH), as well as that of unadjusted doses of unfractionated heparin was recently demonstrated [2,3], allowing the treatment of patients with DVT in an ambulatory setting [4]. However, bed rest remains abundantly prescribed during the first days of treatment. Furthermore, the teaching of many young physicians and nurses continues to include bed rest in the management of patients presenting with DVT or PE.

Bed rest is recommended because of the concern of clot dislodgment by ambulation, causing a potentially fatal PE. This theoretical assumption is so simple that it might be viewed as “evidence-based”. However, it has not been proven scientifically, and is not recommended by guidelines endorsed by scientific committees [5,6]. Conversely, one might argue...
that bed rest is deleterious, by promoting blood stasis and propagation of the thrombus, and lengthens the duration of hospitalization. Indeed, among 4011 patients presenting with acute venous thromboembolisms, Arcelus et al. found immobility to be an important risk factor of lower extremity DVT [7].

To clarify this issue, we conducted a systematic meta-analysis of published studies aimed at comparing ambulation versus bed rest, in addition to anticoagulation, in the management of DVT and PE.

1. Methods

1.1. Literature search

We searched multiple databases up to April 2008, including the Cochrane Central Register of Controlled Trials, Medline, and Embase, using the terms “bed rest”, “ambulation”, “ambulatory treatment”, “ambulatory strategy”, “deep vein thrombosis”, and “pulmonary embolism”. These searched terms were used separately and in combination, in order to identify relevant studies. In addition, the references of listed studies were examined, as well as guidelines, general reviews, and commentaries pertaining to the management of patients with DVT, PE, or both. No language was excluded.

1.2. Study selections

We scrutinized all potentially relevant published articles and abstracts, and included prospective studies that compared initial bed rest versus ambulation, in addition to standard anticoagulation, in patients treated for DVT, PE, or both. Since few randomized studies have been reported, prospective registries were also included in this analysis, if treatment groups and outcomes were clearly described for each group. Additional criteria for inclusion of a study in the meta-analysis included a description of the participants in both groups, and similar anticoagulation regimen in both groups. Finally, the study had to analyze, in both treatment groups, the incidence of ≥1 of the following adverse events: 1) occurrence of new PE, 2) death from all causes, and 3) new or progression of DVT. Two investigators (EM and CM) independently reviewed the studies to assess their suitability for inclusion in the meta-analysis. Disagreements were resolved by consensus. Data from the selected studies were extracted separately by 2 reviewers (NA and CM); disagreements were resolved by consensus.

While the studies included in this meta-analysis applied different methodologies, the information they collected was of similarly high quality with respect to the end-point analyses.

A statement of patient consent or the approval of ethics committee is not provided in our manuscript, as it is not relevant for a meta-analysis.

1.3. Statistical analysis

The likelihood of a publication bias was assessed graphically, using a funnel plot based on data for the occurrence of a new PE. For each study, data regarding the incidence of new PE, new or progression of DVT, and death from all causes in both groups were used to calculate relative risk (RR) and 95% confidence intervals (CI). Heterogeneity was analyzed by means of standard chi square test. When no statistical heterogeneity was identified, the fixed-effect estimate was applied, using the inverse variance method. In case of statistical heterogeneity, a random-effect model was used. All analyses were performed using the STATA, version 9.2 software (StataCorp L, College Station, TX). A p value <0.05 was considered significant.

2. Results

Among a total of 363 references found, 344 were excluded on the basis of their title and abstract; the remaining articles were examined in greater details. Of these, 7 reviews and current opinions of authors, 1 case report, and 1 meta-analysis of 296 patients were not included. In addition, 5 studies were excluded because of duplicate publication (n=1), absence of control group (n=2) and retrospective design (n=2). Thus, we ultimately selected 5 studies, comprising a total of 3048 patients [8–12]. Their main characteristics are shown in Table 1. All studies included patients with proven PE and/or DVT (proximal

<table>
<thead>
<tr>
<th>Study</th>
<th>N/age (years)</th>
<th>Design</th>
<th>Bed rest duration/ambulation date</th>
<th>Anticoagulation regimen</th>
<th>Primary endpoint</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schellong et al. [8]</td>
<td>126/60±15</td>
<td>Randomized</td>
<td>8 days/day 2</td>
<td>Enoxaparin</td>
<td>New PE (scintigraphy on day 0–day 8)</td>
<td>0.25</td>
</tr>
<tr>
<td>Aschwanden et al. [9]</td>
<td>129/65±17</td>
<td>Randomized</td>
<td>4 days/day 0</td>
<td>Dalteparin</td>
<td>New PE (computed tomography scan on day 4)</td>
<td>0.44</td>
</tr>
<tr>
<td>Junger et al. [10]</td>
<td>102/60±15</td>
<td>Randomized</td>
<td>5 days/day 0</td>
<td>Dalteparin</td>
<td>Combined endpoint (new PE or DVT, side-effect, thrombus progression)</td>
<td>0.088</td>
</tr>
<tr>
<td>Partsch and Blatter [12]</td>
<td>45/60±17</td>
<td>Randomized</td>
<td>9 days/day 0</td>
<td>Dalteparin</td>
<td>Combined endpoint (pain, clinical score, leg circumference)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Trujillo-Santos et al. [11]</td>
<td>2650/66</td>
<td>Prospective registry</td>
<td>≥3 days/≤day 3</td>
<td>LMWH</td>
<td>New PE during 15 days of follow-up</td>
<td>ns</td>
</tr>
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*Statistically significant difference in favor of bed rest (bed rest for 48 h in the group with recurrences of pulmonary embolism versus 123 h in the group without recurrences).

PE=pulmonary embolism; DVT=deep vein thrombosis; LMWH=low-molecular-weight heparin.
DVT in all studies but the RIETE registry). One study was a prospective registry including a total of 2650 patients, and 4 were randomized, parallel arms designs including a total of 398 patients. Of these, a single study found a statistical difference in favor of ambulation, using a combined endpoint of changes in pain, of leg circumference and of clinical scores [12].

The funnel plot was not asymmetrical suggesting that there was no bias in publication. In all studies, the anticoagulant was LMWH. In addition, patients were confined to bed for a minimum of 3 days and maximum of 9 days in the group assigned to bed rest. Conversely, the groups assigned to ambulation were allowed to ambulate on day 0 in 3 studies, on day 2 in 1 study, and between day 0 and day 2 in the registry (Table 1).

Fig. 1 shows the results of the meta-analysis with respect to the rates of new PE, ranging between 0.57 and 19%. The absence of heterogeneity among studies (p=0.42) allowed a global analysis. Compared with bed rest, early ambulation in the treatment of PE, DVT, or both, was not associated with a significant risk of new PE (RR 1.03; 95% CI 0.65–1.63; p=0.90; Fig. 1). When considering the combined endpoint of a) occurrence of a new PE, b) progression of DVT, and c) new DVT, no heterogeneity among studies was found. Compared with bed rest, early ambulation was associated with a trend toward a lower event rate (RR 0.79; 95% CI 0.55–1.14; p=0.21; Fig. 2). Finally, when considering the combined endpoint of new PE and overall mortality, there is some heterogeneity in results among studies (p for heterogeneity=0.02), with a prominent contribution made by the registry (26.7%). A random model is warranted; compared with bed rest, early ambulation was not associated with a higher rate events (RR 0.79; 95% CI 0.40–1.56; p=0.50; Fig. 3; random model).

Although no statistical heterogeneity was found among the studies with respect to the rates of new PE, we repeated the analysis after exclusion of the RIETE registry. Compared with bed rest, early ambulation was not associated with a significant risk of new PE (RR 1.10; 95% CI 0.66–1.84; p=0.309; p for heterogeneity=0.309), new PE and overall mortality (heterogeneity 0.642; RR 1.12; 95% CI 0.69–1.82; p=0.642; p for heterogeneity=0.642) or of combined endpoint of new PE±progression of DVT or new DVT (RR 0.87; 95% CI 0.58–1.31; p=0.59; p for heterogeneity=0.65).

3. Discussion

The main observation made in this meta-analysis was the absence of a higher risk of new PE or other adverse clinical
events associated with ambulation, compared with bed rest, in patients undergoing treatment of PE, DVT or both. This finding might be a key with respect to the recommendation of early discharge from hospital and continuation of treatment at home.

Anticoagulation is the main line of treatment of DVT, as well as PE, consisting usually of heparin, promptly followed by oral therapy [2]. The efficacy of LMWH or fixed unfractionated subcutaneous heparin have been recently confirmed, such that continuous intravenous infusions of heparin are no longer recommended, allowing the early discharge of patients from the hospital and continuation of their treatment at home [2–4]. In a systematic review of the Cochrane Database, Schraibman et al. concluded that home treatment of DVT was safe and effective [13]. However, this strategy would be limited by the persistent recommendation of bed rest.

Partsch et al. prospectively measured the incidence of new, symptomatic or asymptomatic PE among 631 patients presenting with DVT, who were treated with LMWH and early mobilization [14]. The rate of new PE detected on a second lung scan, performed on day 10, ranged between 2.7% and 7.0%, depending on whether DVT was proximal or distal. These rates were lower than previously reported, and the authors concluded that patients presenting with DVT who are able to ambulate do not need to be kept at bed rest. This opinion is concordant with a recent retrospective study, which reported the progression of thrombotic disease and the 30-day incidence of PE in 252 patients [15]. In that report, immobilization (hazard ratio 4.58, \( p=0.026 \)) and absence of leg compression (hazard ratio 4.58, \( p=0.009 \)) were the only independent predictors of the clinical endpoint. In contrast, a retrospective study suggested that bed rest for 48 to 72 h should be recommended to patients with DVT to minimize the risk of a new PE [16]. That study, however, was limited by its retrospective design and by its endpoint, which compared the mean period of bed rest imposed to patients who did, versus patients who did not develop a new PE during follow-up. In a meta-analysis published in 2004, early mobilization, compared to bed rest, was not associated with an increased risk of new PE. However, that analysis was limited to 3 studies, including 296 patients [17].

This inconclusive review of all published studies prompted us to perform a new meta-analysis. Our exhaustive search of the literature identified 4 randomized studies and 1 registry (representing over 3000 patients), all of which were methodologically acceptable, including prospective design and proper reporting of patient characteristics and outcomes in each treatment group. In addition, all but one study examined the incidence of new PE diagnosed by lung computed tomography scan, scintigraphy, or both. We omitted multicenter trials that compared home versus in-hospital treatment of DVT [2,4]. While they showed that home treatment was safe, they included no detail regarding mobilization, though one may assume that the majority of patients managed at home were mobilized early.

The presence of a proximal vena cava thrombus, a floating thrombus, or both, is considered to represent a major risk of recurrent PE and, perhaps a formal contraindication to ambulation. In addition, the implantation of vena cava filters was widely advocated a few years ago [18–20]. However, 21 patients with vena cava thrombus or floating thrombus were included in the database of this meta-analysis [9,12]. In addition, the prevalence of floating thrombi among patients with DVT is very low, and their existence has even been questioned [21]. Finally, recent studies suggest that the evolution is usually toward attachment or regression of the thrombus, and is not associated with an increased risk of new PE [22,23]. Therefore, our observations seem to apply to this subgroup of patients as well.

Most current recommendations mention neither bed rest nor early ambulation for patients presenting with DVT or PE [5]. The American College of Chest Physicians, however, briefly recommends early ambulation in their report, though do not mention it in their conclusions [6]. The issue of early ambulation is often raised in the routine care of thromboembolism. Our meta-analysis may therefore, help practitioners in their decision-making process.

Finally, early ambulation has other beneficial effects by alleviating pain, improving the quality of life, and lowering the rate of post-thrombotic syndrome [15,24,25]. Since it may allow home treatment or early discharge from the hospital, it might be cost-effective.

### 3.1. Study limitations

Our study has several limitations. First, randomized studies and prospective registries that satisfied our inclusion criteria were included in our meta-analysis. We recognize that, in the RIETE registry, patients who were allowed to ambulate were less severely ill than patients confined to bed. Cancer, recent surgery, or use of corticosteroids were more prevalent in patients with DVT who were at bed rest, and more patients with PE confined to bed had an arterial PaO\(_2\) < 60 mmHg [11]. However, we also re-calculated the risk ratios of outcome after the exclusion of this registry. Our results show that early ambulation, when compared to bed rest, was not associated with an increased risk of new PE, new PE and overall mortality, or new PE and new or progression of DVT. Second, the timing of ambulation was not precisely the same in all studies, ranging from day 0 to day 2. Since it was allowed as early as day 0 in 3 studies, one might consider that “early” ambulation is possible as soon as a level of effective anticoagulation has been reached. Third, we did not analyze separately patients presenting with PE versus DVT at the time of inclusion into the respective studies. Our aim was to analyze the outcomes of all patients presenting with venous thromboembolism, and we assumed that a distinction between PE and DVT was not relevant. This is supported by several studies, including some selected for our meta-analysis, which showed the presence of a PE in approximately 50% of patients with DVT, regardless of
symptoms [10,12], and the presence of a DVT in 36% of patients with PE [17]. Fourth, the patients were treated with similar anticoagulant regimens in all studies. However, the patients in the “ambulatory groups” might have been treated more often with compression or elastic stockings. Although we did not consider this among major factors in the risk-reduction against new PE, it may, nevertheless, be viewed as a limitation. Fifth, except for the RIETE registry, patients with massive PE had been excluded from the studies included in our analysis. However, very prompt ambulation is unlikely to be relevant in patients whose hemodynamic status is highly unstable. Finally, most studies included in our analyses included symptomatic as well asymptomatic PE detected on systematic examinations. While symptomatic PE is probably the most clinically pertinent endpoint, the inclusion of all new PE was appropriate since our aim was to examine the risk associated with a strategy that recommends early ambulation.

4. Conclusions

Although early ambulation is rarely recommended as part of the initial management of thromboembolic disorders, this meta-analysis did not find that it was associated with a higher risk of a new PE or other adverse outcomes than bed rest. Furthermore, a trend toward a lower mortality and new or progression of DVT was observed among patients managed with early ambulation, as opposed to initial bed rest. These results indicate that initial bed rest is not a recommendation based on evidence, and that is should no longer be part of the management or teachings of thromboembolic disorders. We recommend that early ambulation should be considered in these patients, as soon as a level of effective anticoagulation has been reached.

References