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Full Length Article

Meta-analysis on anticoagulation and prevention of thrombosis and mortality among patients with lung cancer

H.E. Fuentes [a], D.M. Oramas [b], L.H. Paz [a], A.I. Casanegra [c], A.S. Mansfield [d], A.J. Tafur [e,*]

[a] Department of Internal Medicine, John Stroger Jr. Hospital, Chicago, IL, United States
[b] Department of Pathology, University of Illinois at Chicago, Chicago, IL, United States
[c] Department of Cardiology - Vascular Medicine, Mayo Clinic, Rochester, MN, United States
[d] Division of Medical Oncology, Mayo Clinic, Rochester, MN, United States
[e] Cardiology - Vascular Medicine, Northshore University Healthsystem, Evanston, IL, United States

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ABSTRACT

Background: Venous thromboembolism (Wickham et al., 2012 [1]) is a leading cause of morbidity and mortality among patients with cancer; however, primary thromboprophylaxis is not routinely recommended. We performed a systematic review and meta-analysis of randomized control trials (RCTs) to measure the impact of primary VTE prevention and its effect on mortality among patients with lung cancer.
Methods: With assistance from a master librarian, we searched Ovid, Scopus, DARE, CINAHL, MEDLINE, EMBASE, EBM reviews-Cochrane database of systematic reviews, EBM reviews-ACP journal, and EBM Reviews-Databases for relevant studies following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We included articles addressing the role of anticoagulation in patients with lung cancer for primary VTE prevention for outpatients. The clinical outcomes were VTE occurrence, all-cause mortality, major and clinically relevant non-major bleeding. The results are presented as odds ratio (OR) and data were analyzed using R and R META package (Version 0.8–2, Author: Guido Schwarzer).
Results: Eleven studies with 5107 patients were included for the final analysis. We found 50% lower VTE occurrence in the prophylaxis group with low molecular weight heparin (LMWH) (OR: 0.50; 95% Confidence Interval (CI): 0.38–0.66; I2: 0%) without an increased bleeding risk (OR: 2.03; 95% CI: 0.78–5.25; I2: 71.1%). We found a mortality benefit when we grouped all VTE prevention modalities [LMWH, Warfarin, unfractionated heparin (UFH)] (OR: 0.75; 95% CI: 0.58–0.96; I2: 18.4%), but no significant difference when LMWH (OR: 0.74; 95% CI: 0.49–1.11; I2: 56.9%) and warfarin were analyzed individually (OR: 0.75; 95% CI: 0.47–1.21; I2: 0%). We found higher odds of bleeding combining all treatment modalities (OR: 3.06; 95% CI: 1.64–5.72; I2: 64.4%) with the greatest occurrence in the warfarin group (OR: 5.42; 95% CI: 3.48–8.45; I2: 45.7%).
Conclusion: Primary VTE prophylaxis with LMWH reduces the occurrence of VTE among ambulatory patients with lung cancer, without apparent increase in bleeding risk. There is a measurable mortality benefit of anticoagulation strategies that remains elusive when the analysis is restricted to a single agent.

1. Introduction

Lung cancer is the leading cause of cancer death in the United States, accounting for 27% of cancer deaths in 2016 among men and 26% in women [2]. Worldwide, 1.8 million new cases of lung cancer were diagnosed in 2012, and approximately 1.6 million lung cancer deaths occurred the same year [3,4]. Venous thromboembolism [1] including deep vein thrombosis (DVT) and pulmonary embolism (PE) is a preventable and potentially lethal complication among patients with lung cancer; moreover, early events are an independent predictor of poor survival [5,6].

In patients with lung cancer, the incidence of VTE is 22 times higher than the general population, and 7 times higher than in patients with other malignancies [7]. Furthermore, the risk of thrombosis increases by 2.2-folds in patients undergoing chemotherapy when compared to patients with cancer not on this treatment modality [8,9]. Therefore, strategies targeting primary thromboprophylaxis may have a positive impact in both survival and quality of life.

Despite the benefit of outpatient thromboprophylaxis in patients with cancer while on chemotherapy [6,10,11] primary VTE prevention in patients with lung cancer is not routinely recommended [12]. Consequently, we performed a systematic literature review and meta-analysis of the applicable studies encompassing patients with lung cancer

* Corresponding author at: Vascular Medicine, NorthShore University Healthsystem, 2650 Ridge Ave, Evanston, IL 60201, United States.
E-mail address: atafur@northshore.org (A.J. Tafur).

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undergoing chemotherapy and prophylactic anticoagulation, to measure the impact of primary prevention on VTE occurrence and its effect on mortality among these patients.

2. Methods

2.1. Literature search

With the assistance of a master librarian, we conducted a comprehensive search for studies that included pharmacological primary thromboprophylaxis in patients with lung cancer receiving chemotherapy in ambulatory clinics. We searched the electronic databases of Ovid, Scopus, DARE, CINAHL, MEDLINE (FROM 1946), EMBASE (from 1947), EBM reviews-Cochrane database of systematic reviews (from 2005), EBM reviews-ACP journal (from 1991), EBM Reviews-Databases of abstracts of reviews of effect for articles that met our criteria, with the databases being last accessed on 05 May 2016. We searched and reviewed the candidate abstract and manuscripts following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. We applied no language restrictions. The search strategies were as follow: ((("Neoplasms") AND ((((("Venous Thromboembolism") OR "Thrombophlebitis") OR "Venous Thrombosis") OR "Thromboembolism"))) AND ("prevention and control" OR "anticoagulant" OR "low-molecular-weight heparin (LMWH)" OR "warfarin" OR "vitamin K antagonist" (VKA) OR "Heparin").

2.2. Study eligibility

Two authors (HF, DO) independently screened the title and abstract of identified citations for potential eligibility. Disparities were resolved with a tie breaker (AT, LP). We included randomized and non-randomized controls trials, prospective and retrospective trials related to our primary requirements. Anticoagulants used for prophylaxis could include unfractionated heparin (UFH), low molecular or ultra-low molecular heparin (ULMWH), direct factor Xa inhibitors, thrombin inhibitors or vitamin K antagonist. We excluded case reports, review articles, guidelines, editorials and meta-analyses. Only manuscripts with extractable primary data among patients with lung cancer were included in the final analysis.

2.3. Outcome definition

The main efficacy outcome was VTE. These events could be asymptomatic or symptomatic and included objectively documented PE or DVT. DVT and PE occurring in the same patient were recorded as single event. Arterial embolic events were not counted. Diagnosis of VTE could be made with Doppler imaging, ventilation/perfusion scan, CT angiography, venography, angiography or autopsy. The secondary efficacy outcome was all-cause mortality. The main safety outcome was major bleeding, as defined in by the original authors and all bleeding.

2.4. Data extraction

We followed the same hierarchy of independent data selection as in the initial screening. The collected information included [14]: type of study, (2) sample size, (3) type and stage of lung cancer, (4) performance status, (5) intervention (e.g. dose, route, duration and type of anticoagulation) (5) follow up, (6) clinical outcomes. We did not abstract mortality data from Kaplan Meir curves in the absence of provided censoring information. The authors of the included studies were contacted for additional information if there were insufficient data for analysis.

2.5. Quality assessment

We summarized the methodological quality of each study as high, medium or low likelihood of bias according to randomization technique, allocation concealment, comparability of groups at baseline, blinding, completeness of follow-up, assessment of incomplete data and validity of outcomes. We accounted for attrition, performance, and detection bias as recommended [15]. Low bias risk was equivalent to "unlikely to seriously alter results"; medium risk implied "bias that raises some doubt about results"; high risk was deemed to "seriously weaken confidence in results".

2.6. Statistical analysis

We calculated a Q statistic and a formal test of heterogeneity [16]. Given our findings of heterogenous results we limited the analysis to a random-effects model. The I^2 statistics was used to quantify the heterogeneity across the studies [17], with $I^2 < 25\%$, 25–75%, and >75% to represent low, moderate, and high degree of heterogeneity. We performed an influence analysis estimating the pooled effect sizes after leaving each study out. Pre-specified sub group analyses included anticoagulation agent (Warfarin, low molecular weight heparin). There were insufficient data to perform a pooled analysis by stage. Data were analyzed using R (R Development Core Team, www.R-project.org), R META package (Version 0.8–2, Author: Guido Schwarzer).

All authors had access to the analysis and participated in the interpretation.

3. Results

3.1. Included studies

The literature search yielded a total of 9831 articles, from which 2108 were selected after removing duplicates. Title and abstract screening identified 2016 citations not relevant to our study aim. After full-text review of the remaining articles, we included 11 randomized control trials of 5107 patients with lung cancer into the meta-analysis [18–28]. A flow chart of the evaluation of the studies is shown in Fig. 1.

Nine of the included studies recruited patients with lung cancer only [19–26,28]; the others enrolled patients with different types of cancer in addition to lung cancer [18,27]. Among those with lung cancer only, seven studied patients with small cell lung cancer (SCLC) [19,20,22,23,25,26,28], one studied non-small cell lung cancer (NSCLC) [21] and one included both histological subtypes [24]. Two studies [23,25] addressed the effect of anticoagulation in patients with SCLC and limited disease, whereas only one study evaluated the effect of anticoagulation in patients with extensive disease [20]. The remaining studies of SCLC included patients in both stages [19,22,26,28]. Six studies assessed the effect of LMWH in lung cancer. However, the type of LMWH and duration of treatment differed in each study, ranging from twelve to forty-six weeks of subcutaneous dalteparin, semuloparin, certoparin, bemiparin and nadroparin [18,19,21,23,24,27]. Four studies assessed the effect of warfarin and one the effect of UFH (Table 1).

We found that the duration, timing and dosing of primary thromboprophylaxis differed among all the included studies.

3.2. VTE prevention

Five studies provided information regarding thromboembolic events [18,19,21,23,24] from which we pooled a total of 241 (6%) VTE events. These studies used LMWH and included both histological subtypes of lung cancer. We detected no significant heterogeneity and a lower rate of VTE in the prophylaxis group (Odds Ratio [OR]: 0.50; 95% Confidence Interval [CI]: 0.38–0.66; I2: 0%) (Fig. 2). In the influence analysis, no single study changed the main results (data not shown). On a