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Complications - Other

Pulmonary Embolism Rates Following Total Hip Arthroplasty With Prophylactic Anticoagulation: Some Pulmonary Emboli Cannot Be Avoided

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ABSTRACT

Background: A symptomatic pulmonary embolism (PE) after total joint arthroplasty has been described as a "never event." Despite potent anticoagulants and improvements in patient care, PE continues to occur following total hip arthroplasty (THA). This study evaluates symptomatic PE rates over time in THA patients enrolled in multicenter randomized clinical trials (RCTs) assessing the efficacy of venous thromboembolism prophylaxis regimens.

Methods: The MEDLINE and Cochrane Central Register of Controlled Trials were searched to identify clinical trials assessing prophylactic anticoagulation in patients undergoing THA between January 1995 and December 2015. Inclusion criteria consisted of RCTs evaluating prophylactic anticoagulation in patients undergoing THA. A random effect model was used to combine PE rates across studies.

Results: A total of 21 studies (34,764 patients) were included. Patients were administered low molecular weight heparin (13,590 patients), oral factor Xa inhibitors (6609 patients), oral direct thrombin inhibitors (5965 patients), indirect factors Xa/IIa inhibitors (3444 patients), aspirin (2427 patients), and warfarin (489 patients). Mobile compression was used in 199 patients, and placebo was used in 2041 patients. Across all included studies, the estimated PE rate was 0.21% (95% confidence interval: 0.13%, 0.32%). Between 1997 and 2013, the proportion of PEs did not change in regression analysis.

Conclusion: Although the PE rate was low, it was consistent throughout the 17 years spanning these RCTs, which excluded patients with significant morbidity. These results suggest that even healthy THA patients receiving aggressive anticoagulation still have a risk for PE, and the "never event" designation requires reassessment.

Symptomatic pulmonary embolism (PE) is a serious and potentially fatal complication of total hip arthroplasty (THA). The Centers for Medicare and Medicaid Services considers a PE following total joint arthroplasty a "never event," a term used to define "serious, preventable, and costly medical errors." [1] While presumed ultimately preventable, symptomatic venous thromboembolism (VTE) occurs in patients following THA. The in-hospital incidence of a symptomatic VTE has been reported to be approximately 0.5% following total and partial hip arthroplasty procedures [2]. In the 3-month period following surgery, the symptomatic VTE rate has been estimated to be between 2% and 5% in THA patients [3].

Estimates of incidence rates of symptomatic VTEs have been largely derived through systematic reviews of the literature [2]. These reviews encompass 2 decades of research during which significant advances have been made with respect to the perioperative and operative management of THA patients. Over the past 15 years, the efficacy of multiple chemoprophylaxis agents have been assessed in multicenter randomized trials. Most of these studies have evaluated new agents vs the low molecular weight heparin (LMWH). In general, these agents have been found to be as effective as LMWH in reducing the overall VTE

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(symptomatic and asymptomatic) rates. In addition to these trials, improved knowledge of risk factors and care pathways, including the use of spinal anesthesia, early mobilization, and decreased length of stay, may have created a perception that the symptomatic PE rate has decreased over time.

The purpose of this systematic review was 2-fold: (1) to determine the proportion of symptomatic PEs among patients enrolled in multicenter randomized controlled trials assessing the efficacy of various venous thromboembolic prophylaxis regimens and (2) to evaluate whether the prevalence of PEs has changed over time. Our hypothesis was the improvements in both the care of patients and the prophylaxis available for prevention of VTE has lead to a decrease in the proportion of PEs over time.

Materials and Methods

Eligibility Criteria/Inclusion Criteria

Articles written in the English language were evaluated for inclusion. To be included in the analysis, a study had to meet the following criteria: (1) included patients undergoing elective THA; (2) assessed VTE prophylaxis regimens including apixaban, ardeparin, aspirin, dabigatran, dalteparin, enoxaparin, fondaparinux, mobile compression, rivaroxaban, warfarin, or ximelagatran; (3) utilized a prospective multicenter randomized clinical trial (RCT) design; and (4) explicitly described the number of symptomatic PEs occurring in each treatment arm in patients undergoing THA.

Literature Search

A single investigator conducted a comprehensive literature search of the MEDLINE database via PubMed and the Cochrane Central Register of Controlled Trials database via the Cochrane Register of Studies Online (CRSO). All relevant articles published between January 1995 and December 2015 were identified. The search algorithm used for PubMed included the following key words: (hip, hip arthroplasty, hip replacement) and (thrombosis, thromboembolism, pulmonary embolism) and (prophylaxis or thromboprophylaxis) and (apixaban or ardeparin or aspirin or dabigatran or dalteparin or fondaparinux or mobile compression or rivaroxaban or ximelagatran). The search algorithm was found to be too restrictive for the CRSO based on a low number of returned articles. Therefore, the search algorithm was broadened to the following: (hip arthroplasty, hip replacement) and (apixaban or ardeparin or aspirin or dabigatran or dalteparin or fondaparinux or mobile compression or rivaroxaban or ximelagatran). In addition, references cited in the last 6 editions of "Prevention of Venous Thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines" were hand searched for relevant articles. These clinical practice guidelines were published between 1995 and 2012 [3-8].

Study Selection

Two study investigators screened the titles and abstracts of all studies identified in the literature search. After initial screening, full-text articles were retrieved and 3 reviewers independently assessed the eligibility of each study for final inclusion. Discrepancies were discussed as a group and resolved by consensus.

Data Extraction

A single investigator independently abstracted all relevant data. Prior to data extraction, predetermined data were categorized into 3 categories: study characteristics, efficacy outcomes, and methodological quality. Study characteristics included the thromboprophylactic regimen that had been assessed, the dose of each agent, the administration schedule of each agent, the number of THA patients receiving each agent, the duration of time during which the patients were observed and followed up, and the year the article was published. Abstracted efficacy outcomes included the number of symptomatic nonfatal PE and symptomatic fatal PE as well as diagnostic methods used to confirm PEs. Articles that failed to explicitly parse out the number of symptomatic PEs from other VTEs were omitted from the final analysis.

Risk-of-Bias Assessment

The Cochrane Risk of Bias tool was used to grade methodological quality of the RCTs. Two reviewers assessed the methodological quality of each study using the Cochrane Risk of Bias tool. This tool evaluates 7 domains of a clinical trial (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias). Each of these domains is reviewed, and a judgment is made as to whether there is a low, high, or unclear risk of bias based on the available information. Any conflicting scores were resolved by discussing the item in question. Agreement between the 2 reviewers was assessed with the kappa statistic. An a priori kappa value of 0.7 was selected as adequate agreement between raters. Risk of bias summary graph was constructed using Review Manager (RevMan) (Computer program), version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Data Synthesis and Evaluation of Heterogeneity

The decision to pool data was based on the availability of randomized control trials conducted in uniform study groups (patients undergoing elective THA). We conducted a meta-analysis of the pooled proportions of symptomatic PEs in the included studies. A random-effects model using the method of DerSimonian and Laird was used to calculate the pooled estimated proportions and 95% confidence intervals (CIs). The Freeman-Tukey Double Arcsine Transformation was applied to allow studies with 0 symptomatic PE events to be included in the analysis. Heterogeneity between the studies was quantified with the I^2 statistic. An I^2 value $< 25\%$ was selected to represent low heterogeneity whereas a value $> 75\%$ was selected to represent high heterogeneity. The effect of time, as a continuous variable (the year of study publication) and at 2 separate cutoffs, on the proportion of symptomatic PEs was explored using random-effects meta-regression. Subgroup analysis was performed to explore whether the methodological quality of the studies or the types of prophylaxis that were used were potential contributors to heterogeneity. The alpha level of all statistics was set at 0.05. All statistical analysis was performed using Stata 12 (StataCorp. 2011, Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

Results

Literature Search

The initial PubMed and CRSO searches returned 134 and 157 articles, respectively. Searching the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines yielded 72 articles. After removing duplicated citations, 291 unique citations were identified, and their abstracts were retrieved. Of the 291 abstracts screened, 28 articles did not discuss THA patients, 19 did not include one of the predetermined thromboprophylactic agents of interest, and 215 were not multicenter RCTs. For the remaining 29