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The occurrence of venous thromboembolism in cancer patients following major surgery

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ABSTRACT

Background: Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is common in cancer patients and surgery is an important risk factor.
Objective: To describe the occurrence of VTE in cancer patients following major surgery and to determine the risk of VTE recurrence.
Methods: Using the administrative health claims (RAMQ) and hospital discharge (MED-ECHO) databases of the province of Québec, Canada, we constructed a cohort of all individuals with incident VTE between January 1, 1994 and December 31, 2004 diagnosed with cancer and who had major surgery in the 91 days prior to the VTE. The timing of VTE after surgery was determined. Recurrent VTE was defined as re-hospitalization with a principal discharge diagnosis of VTE.
Results: Our cohort consisted of 2706 cancer patients with VTE following major surgery. The mean age was 65.9 years (Standard Deviation 12.6) and 54% were female. The median duration of surgical hospitalization was 18 days (range 1-735 days). The median time to VTE following surgery was 15 days (range 1-659 days), and 34% of VTE events were diagnosed after hospital discharge. The 1-year cumulative rate of recurrence was 6.7% (95% CI 5.7, 7.9) and the 5-year cumulative rate was 12.6% (95% CI 10.7, 14.7). Increasing comorbidity (adjusted hazard ratio (HR) 2.49, 95% CI 1.58-3.95) and VTE diagnosed after hospital discharge (adjusted HR 1.48, 95% CI 1.09-2.01) were associated with recurrence.
Conclusions: A significant proportion of VTE episodes among surgical patients with cancer are diagnosed after discharge from hospital. This suggests that surgical patients with cancer are at risk for VTE beyond the immediate postoperative period.

Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is common in cancer patients, especially following major surgery. Compared to patients without cancer, cancer patients have twice the risk of VTE after surgery [1], with reported incidences of asymptomatic calf vein DVT of 40-80%, proximal DVT of 10-20%, PE of 4-10% and fatal PE of 1-5% without perioperative thromboprophylaxis [1]. The risk period for VTE following major surgery in cancer patients has not been well-studied. Indirect evidence largely from prospective studies of patients followed for VTE after major surgery suggests that the risk likely extends beyond the immediate postoperative period and long after discharge from hospital [2–4]. For example, among 947 454 middle aged women in the United Kingdom recruited in 1996-2001 and followed for a mean of 6.2 years by record linkage to routinely collected data on hospital admissions, women undergoing inpatient and same-day surgery were 70 times more likely to be admitted for VTE in the first six weeks after inpatient surgery compared to women not having surgery, and the relative risk of VTE remained substantially elevated up to 12 weeks following inpatient surgery (Relative risk (RR) 19.6; 95% confidence interval (CI) 16.6, 23.1) [5]. Given the high risk of postoperative thrombosis in cancer patients, understanding the timing of postoperative VTE in this population is important for clinicians especially if contemplating extended thromboprophylaxis beyond the immediate postoperative period. Moreover, there is a lack of data on the risk of recurrence in cancer patients who have been diagnosed with post-operative VTE. As a result, we aimed to describe the occurrence of incident VTE in a large non-select population of cancer patients following major surgery and to determine the risk of recurrence among cancer patients with postoperative VTE.

Methods

Study Design

This was a population-based retrospective study using the linked administrative healthcare databases of the province of Québec, Canada to identify a cohort of Québec residents with an incident VTE within three months of major surgery from January 1, 1994 to December 31,

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2004 and followed forward in time for the occurrence of recurrent VTE until the earliest of either death, termination of health coverage or end of study period (December 31, 2005).

Description of Databases

We used the linked databases of the Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière (MED-ECHO) and the Régie de l'Assurance Maladie du Québec (RAMQ). MED-ECHO contains information on all acute care hospitalizations in Québec including one primary and up to 15 secondary discharge diagnoses classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, and up to eight surgical and diagnostic procedure codes according to the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP) [6]. RAMQ manages the provincial public health and prescription drug insurance programs, and maintains linked beneficiary, in- and out-of hospital medical services, and outpatient prescription databases. RAMQ health insurance coverage is compulsory for every resident or temporary resident of Québec. Coverage ceases if the beneficiary dies or is no longer a resident of Québec. Every beneficiary is assigned a unique RAMQ health insurance number, which enables electronic record linkage of RAMQ's databases to MED-ECHO. The beneficiary's database includes the date of birth and death. The medical services claims database contains all physician reimbursement claims for in-hospital and ambulatory health services (physician visits, surgical procedures, and diagnostic procedures). The diagnostic codes are classified according to ICD-9-CM and all surgical and diagnostic procedure codes are compliant with the CCP [6]. RAMQ medical services claims data were found to be 87% and 78% sensitive for the diagnosis of DVT and PE, respectively [7]. The prescription database contains data on all dispensed medications including drug name and drug identification number (DIN). Drugs dispensed to patients during hospitalization and over-the-counter drugs are not included. Unlike health coverage, RAMQ prescription coverage is not universal and covers persons aged 65 years or older and residents less than 65 years of age, who are welfare recipients or do not have access to private insurance. The identifying and recorded prescription information in the RAMQ prescription databases has been validated [8].

Cohort Definition

The source population consisted of all RAMQ beneficiaries between January 1, 1994 and December 31, 2004 with a medical service associated with an ICD-9-CM code for VTE (index VTE), at least 12 months of RAMQ coverage preceding the VTE, and without a prior VTE code. From the source population of Québec residents with incident VTE, we identified our study population which consisted of all subjects with a primary (condition occasioning admission to hospital) or secondary (condition arising during hospitalization) hospital discharge VTE diagnosis in MED-ECHO together with a hospital stay of at least two days duration [9,10], a hospital discharge diagnosis for cancer during or up to 12 months preceding the VTE hospitalization, and a CCP procedure code for major surgery during or up to 91 days prior to the VTE hospitalization. Major surgery included abdominal, gynecologic, thoracic, genito-urinary, orthopedic, and neurosurgery and were identified using CCP codes. Deep vein thrombosis (DVT) was defined using the ICD-9-CM codes for thrombophlebitis and venous thrombosis of the lower extremity and include 451.0, 451.1, 451.2, 451.8, 451.9, 453.1, 453.2, 453.4, 453.8, 453.9, 671.3, 671.4, 671.9, and 997.2. Pulmonary embolism (PE) was defined using ICD-9-CM codes 415.0, 415.1, 673.2, 673.8, and 997.3. RAMQ and MED-ECHO electronically record ICD-9-CM codes up to four digits and only report to the first decimal point. If both DVT and PE codes were identified in the discharge diagnosis fields, then the case was categorized as having DVT with PE.

The date of hospital admission was considered the date of VTE occurrence for all cases admitted with a principal diagnosis of VTE. Among patients with a secondary discharge diagnosis of VTE and an associated diagnostic VTE procedure test code (e.g. Doppler ultrasonography, ventilation-perfusion scan), the procedure date was considered the date of VTE occurrence. If a procedure date was not recorded, the median hospital day was used to define the date of VTE occurrence [11]. We obtained RAMQ and MED-ECHO data up to 12 months preceding the VTE diagnosis and until RAMQ coverage termination, death, or end of study (December 31, 2005).

Cohort Characteristics

For all subjects, we determined patient demographics including age and sex, cancer type, surgery type and date of surgery, and the presence of an out-patient prescription for an anticoagulant (oral vitamin K antagonists, low molecular weight heparin, or unfractionated heparin) following discharge from the surgical hospitalization. We also determined the presence of co-morbid conditions using the modified Charlson index [12], which was based on the presence or absence of 17 different conditions defined by ICD-9-CM codes at the time of and up to 12 months preceding the VTE. Conditions associated with VTE treatment (e.g. gastrointestinal bleeding) present during the VTE hospitalization were excluded from the index calculation.

VTE Recurrence

VTE recurrence was defined as a hospitalization of at least two days duration with a principle discharge diagnosis of VTE at least one day following discharge from the index VTE hospitalization [13,14]. Date of recurrence was the date of admission for the re-hospitalization. The same ICD-9 CM codes used to define index VTE were used to identify recurrent VTE.

Statistical Analysis

Descriptive statistics included number and percent for categorical variables and mean and standard deviation (SD) for continuous variables. Categorical data were compared using the chi-square test, and continuous data presented as means were compared using t-tests. All P values <0.05 were considered statistically significant. Time (days, median, range) to VTE following surgery was determined and VTE was categorized as occurring during surgical hospitalization or following discharge. Survival-time methods were used to analyze the time to recurrent VTE. Follow up began on the date of index VTE and ended at the earliest of death, first recurrent VTE, end of RAMQ membership, or end of study (December 31, 2005). Univariate and multivariate Cox proportional hazards models were used to analyze the association of patient characteristics with risk of recurrence. Analyses were adjusted for potentially confounding factors. Hazards ratio (HR) with 95% CI are reported. Analyses were performed using Stata [15].

Ethics Approval

The study protocol was approved by the Commission d'Accès à l'Information du Québec and the Research Ethics Office of the Jewish General Hospital, Montreal Québec. RAMQ was responsible for the linkage and preparation of the datasets. Prior to delivery of the datasets to the investigators, personal identifiers were removed.

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