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Full Length Article

Risk factors for venous thromboembolism after acute trauma: A population-based case-cohort study☆,☆☆,★

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ABSTRACT

Background: Predictors of venous thromboembolism (VTE) after trauma are uncertain.
Objective: To identify independent predictors of VTE after acute trauma.
Methods: Using Rochester Epidemiology Project (REP) resources, we identified all Olmsted County, MN residents with objectively-diagnosed incident VTE within 92 days after hospitalization for acute trauma over the 18-year period, 1988–2005. We also identified all Olmsted County residents hospitalized for acute trauma over this time period and chose one to two residents frequency-matched to VTE cases on sex, event year group and ICD-9-CM trauma code predictive of surgery. In a case-cohort study, demographic, baseline and time-dependent characteristics were tested as predictors of VTE after trauma using Cox proportional hazards modeling.
Results: Among 200 incident VTE cases, the median (interquartile range) time from trauma to VTE was 18 (6, 41) days. Of these, 62% cases developed VTE after hospital discharge. In a multiple variable model including 370 cohort members, patient age at injury, male sex, increasing injury severity as reflected by the Trauma Mortality Prediction Model (TMPM) Mortality Score, immobility prior to trauma, soft tissue leg injury, and prior superficial vein thrombosis were independent predictors of VTE (C-statistic = 0.78).
Conclusions: We have identified clinical characteristics which can identify patients at increased risk for VTE after acute trauma, independent of surgery. Almost two thirds of all incident VTE events occurred after initial hospital discharge (18 day median time from trauma to VTE) which questions current practice of not extending VTE prophylaxis beyond hospital discharge.

1. Introduction

Hospitalization for acute trauma is an independent risk factor for incident VTE (hazard ratio [HR] = 4.6) [1] and accounts for about 12% of all incident VTE occurring in the community [2]. Failure to provide appropriate VTE prophylaxis to hospitalized, at-risk patients is considered a medical error by the Institute of Medicine [3]. However, acute trauma patients also are at increased risk for a bleeding complication related to VTE chemoprophylaxis such that one would prefer to target such prophylaxis to those high VTE-risk trauma patients who would benefit most. Several studies have identified risk factors for VTE during hospitalization for trauma [4–7]. However, the duration of hospitalization after trauma has decreased such that many trauma-related VTE events now occur after hospital discharge. Independent predictors of VTE, both during and after hospitalization for acute trauma, are uncertain [8]. To address this important gap in knowledge, we performed a population-based case-cohort study and tested demographic, pre-injury and in-hospital characteristics as potential predictors of incident symptomatic VTE among patients with hospitalization for acute trauma.

2. Methods

2.1. Study design and setting

This population-based case-cohort study was conducted in Olmsted County, Minnesota (2010 census population = 144,248). Olmsted County provides a unique opportunity for investigating risk factors for

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Table 1
Demographic and baseline characteristics of venous thromboembolism (VTE) cases and cohort members.

Characteristic	VTE cases (n = 200)	Cohort members (n = 370)	P-value
Age at Trauma, median (IQR); years	74 (54, 85)	58 (33, 81)	<0.001[a]
Male sex; n (%)	79 (40)	138 (37)	0.605[b]
BMI, median (IQR); kg/m[b]	26 (23, 30)	25 (22, 29)	0.004[a]
Trauma Mortality Prediction Model (TMPM), median (IQR); %	1.2 (0.06, 2.0)	0.8 (0.3, 1.7)	0.188[a]
Mechanical prophylaxis; n (%)	86 (43)	113 (31)	0.003[b]
Arm fracture	24 (13%)	76 (20.5%)	0.010[b]
Leg fracture	96 (48%)	165 (45%)	0.436[b]
Chemoprophylaxis; n (%)	103 (52)	145 (39)	0.005[b]
IVC filter after trauma; n (%)	9 (4.5)	2 (0.5)	0.002[c]

[a] Wilcoxon rank sum test.
[b] Chi-square test.
[c] Fisher's exact test.

VTE after hospitalization for trauma. Mayo Clinic, together with Olmsted Medical Center (OMC) provides essentially all of the trauma medical care delivered to County residents [9–11]. The Rochester Epidemiology Project (REP) medical records-linkage system affords access to comprehensive details regarding all medical care provided to all residents for their entire period of residence in the County. In a comparison to the U.S. Census enumeration for Olmsted County, the REP Census enumeration had excellent validity for every Census year since 1930 [9]. Trauma was defined as major fracture or severe soft tissue injury requiring hospitalization that occurred ≤92 days prior to the incident VTE event as previously reported [1]. The study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

2.2. Study population

Using REP resources, we identified all Olmsted County, MN residents with incident deep vein thrombosis (DVT) and/or pulmonary embolism (PE) as previously described [12,13]. Determination of VTE was based on explicit criteria after review of complete provider-linked medical records by trained experienced nurse abstractors under the direction of a board-certified vascular medicine specialist (JAH). Records were reviewed from date first seen by a REP provider until the either death or last REP encounter. For the purposes of this study, VTE cases were limited to residents with objectively-diagnosed incident DVT and/or PE over the 18-year period, 1988–2005, that occurred within 92 days (365 days divided by 4, or ~3 months) after hospitalization for acute trauma. A deep vein thrombosis (**DVT**; leg, inferior vena cava, hepatic, portal, splenic, mesenteric or renal vein thrombosis) was considered objectively-diagnosed when acute symptoms and signs were present and confirmed by venography, compression venous duplex ultrasonography, impedance plethysmography, computed tomography, magnetic resonance imaging (MRI), pathology examination of thrombus removed at surgery, or autopsy. A pulmonary embolism (PE) was considered objectively-diagnosed when acute symptoms and signs were present and confirmed by pulmonary angiography, ventilation and perfusion lung scan interpreted as high probability for PE, computed tomographic pulmonary angiography, MRI, pathology examination of thrombus removed at surgery, or autopsy. Routine screening for asymptomatic DVT or PE was not performed. Mayo Clinic pathologists performed all autopsy examinations and completed the death certificates. REP resources also were used to identify all Olmsted County residents with hospitalization for acute trauma over the study period, 1988–2005, using an ICD-9-CM trauma code algorithm that was derived and validated using previously-identified Olmsted County residents with incident DVT and/or PE within 92 days after hospitalization for acute trauma [1]. Since we previously identified surgery as an independent VTE risk factor [1], we wished to identify VTE risk factors among acute trauma patients who had surgery. Therefore, we further refined our ICD-9-CM trauma code algorithm in order to stratify residents with trauma into those likely to and those unlikely to require surgery. Each of the injury codes was reviewed by a board-certified trauma surgeon (MSP) and if an ICD-9-CM injury code was associated with an operative intervention at least 20% of the time, the trauma code was considered likely to require surgery. Using this refined algorithm, the list of Olmsted County residents with trauma from 1988–2005 was stratified by likelihood of having surgery. These lists were further stratified by sex and three time periods (i.e., 1988–1993, 1994–1999, 2000–2005), and then residents within each of the 12 lists were randomized. Using these 12 randomized lists, the cohort was selected such that the number of cohort members in each of the 12 strata was at least equal to the number of VTE cases in that stratum. Potential cohort members with a VTE event at any time prior to the trauma event date were excluded. Residents with an ICD-9-CM trauma code that predicted an increased likelihood of requiring surgery and selected to be in the cohort were included regardless of whether they actually underwent surgery.

2.3. Measurements

Using explicit criteria, trained and experienced nurse abstractors reviewed all medical records (inpatient, outpatient, emergency department, nursing home, autopsy, death certificate, etc.) in the community for all cases and cohort members who provided consent to review of their medical records for research purposes; over 95% of residents consented [10,14]. All records were reviewed from date first seen by a REP healthcare provider until the earliest of death or other loss to follow-up, or 92 days after the trauma event date, as previously performed [15]. Data related to surgery were also collected, including number of operations prior to or after admission for trauma, type of operations (general, gynecological, neurologic, orthopedic, cardiac), intraoperative transfusions (type and number of units), and duration and type of anesthesia (Appendix A). Because injury severity scores (ISS) were not uniformly available, we used a validated Trauma Mortality Prediction Model based on anatomic injury scale provided by Dr. Turner Osler [16]. The model weighs each injury code to provide the probability of hospital mortality. For trauma patients who had minor injuries with no injury codes, the lowest mortality score (0.06%) from among the remaining patients with a score was imputed. We have termed this variable as the "Trauma Mortality Prediction Model (TMPM)."

2.4. Statistical analyses

For cases and cohort members, data collection of variables was categorized into the following groups: 1) baseline characteristics present at the trauma event date; 2) baseline characteristics present within 92 days prior to trauma event date; 3) baseline characteristics present at any time prior to the trauma event date; and 4) time-dependent characteristics after the trauma date, censored at VTE event date for cases, and at last follow-up for 92 days after the trauma event date for cohort members. We performed a case-cohort study with weighted cohort sampling by incorporating inverse sampling probability weights in the analysis. Patient demographic and baseline characteristics were

Table 2
Locations of DVTs of cases (53 patients had DVT in multiple locations).

Thrombosis location	Number	Percent
Lower extremity, distal	34	19.7
Lower extremity, proximal	124	71.7
Upper extremity	3	1.7
Jugular/subclavian vein	5	2.9
Inferior vena cava	3	1.7
Portal vein	2	1.2
Renal vein	1	0.6
Other	1	0.6

Missing Information = 7 locations.