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Full Length Article

Incidence and risk factors for venous thromboembolism in patients with acute spinal cord injury: A retrospective study

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ABSTRACT

Introduction: The true incidence of venous thromboembolism (VTE) in patients with acute spinal cord injury (SCI) is unclear. There are limited data on the risk factors associated with VTE in patients with an acute SCI.
Methods: We performed a retrospective chart review of consecutive adult patients with acute SCI. The primary outcome was incidence of symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE) within 90 days. Secondary outcomes were major bleeding, all-cause mortality, and fatal PE. Step-wise Cox modeling was used to identify risk factors for VTE.
Results: A total of 151 patients with acute SCI were included. Median age was 51 (range 17–91 years) and 106 (70%) were males. Of the 151 patients, 17 (11%) had symptomatic VTE (9 PEs, 6 lower extremity DVT, 1 upper extremity DVT, and 1 with DVT and PE). In the univariable analyses, male sex and having other sites of injuries along with SCI were significant risk factors. In stepwise Cox modeling, independent risk factors were other sites of injuries (hazard ratio [HR] 6.07, 95% confidence interval [CI] 1.89–19.47, p = 0.002), age (HR 1.05 per year, 95% CI 1.02–1.08, p = 0.002) and the presence of leg paresis (HR 2.7, 95% CI 0.72–10.54, p = 0.14), whereas hypertension appeared to reduce the risk (HR 0.18, 95% CI 0.04–0.78, p = 0.02).
Conclusions: Symptomatic VTE is a frequent complication in patients with acute SCI. Age and presence of other sites of injuries along with SCI were independent risk factors for symptomatic VTE.

1. Background

Patients with an acute spinal cord injury (SCI) have the highest incidence of venous thromboembolism (VTE) among hospitalized patients [1–2]. VTE is common within the first 3 months after SCI [3]. The overall incidence of symptomatic or asymptomatic deep vein thrombosis (DVT) in untreated SCI patients ranges from 50 to 100%, with the first two weeks following injury having the highest rate [4–5]. Furthermore, pulmonary embolism (PE) is the third most common cause of mortality in patients with SCI with an incidence of fatal PE estimated as high as 5% [6]. VTE after SCI is associated with significant morbidity and mortality for these patients [5]. It is therefore important for these high-risk patients with SCI to receive thromboprophylaxis.

Low molecular weight heparins (LMWHs) have become the most utilized method of venous thromboprophylaxis for patients with acute SCI [6–7]. However, there is lack of high quality studies examining the efficacy of LMWHs in patients with acute SCI. A study by Geerts et al. compared low-dose heparin with LMWH in a cohort of 265 trauma patients, which also included a subgroup of patients with SCI [8]. The authors found that DVT occurred at a significantly higher rate in those receiving low-dose heparin than in the LMWH group. LMWH was reported to be more efficacious than low-dose heparin in trauma patients [9]. Furthermore, a prospective study reported that LMWH was more effective than low-dose heparin in prophylaxis against VTE during rehabilitation after SCI [9]. A recent systematic review and meta-analysis on heparin prophylaxis in patients with SCI concluded that there is lack of high quality studies in this area [5].

Many studies have reported potential risk factors of SCI-associated VTE [3,10–14]. However, the reliability of the data is limited by variability in the duration of follow-up and the diagnostic methods utilized (routine screening versus diagnostic imaging only of symptomatic cases), and heterogeneity in the outcome definitions. Therefore, there is uncertainty about the risk factors and the true incidence of SCI-associated VTE. The American College of Chest Physicians (ACCP) guidelines recommend that all patients with SCI receive thromboprophylaxis (Grade 1A) [15]. However, there is also uncertainty about the appropriate duration and the dose intensity of thromboprophylaxis.

Given the limited available data, our aims were to: 1) evaluate the incidence and risk factors of symptomatic VTE in patients with acute SCI, and 2) investigate the appropriate intensity and duration of VTE prophylaxis in patients with acute SCI.

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2. Materials and methods

2.1. Inclusion and exclusion criteria

A retrospective chart review of consecutive adult patients with acute SCI from 2009 to 2015 was conducted at the Hamilton Health Sciences-General Hospital. Patients were included if they met the following criteria: 1) acute traumatic or non-traumatic SCI; and 2) presenting within 1 week of injury. We excluded patients who were already on therapeutic oral anticoagulation, those who had a short hospital admission (≤7 days), and patients who had early transfer to a different hospital location (≤30 days from the initial admission) without possibility to follow up. Patients who had a short hospital admission were excluded as they had a mild degree of SCI and were mobilizing well when discharged home.

The study was approved by the Hamilton Integrated Research Ethics Board without need for informed consent.

2.2. Baseline characteristics

Demographic and clinical characteristics were collected, including factors previously suggested as being predictive of acute SCI-associated VTE: age, gender, body weight, year of injury, presence of spinal fracture, degree of neurological impairment, level of injury, presence of other sites of injury, length of hospital stay (LOS), and co-morbidities including hypertension, diabetes mellitus, coronary artery disease (CAD), cerebrovascular accident (CVA), chronic kidney disease, respiratory diseases, and cancer. Body weight was available for 107 patients and missing for the remaining 44 patients.

Presence of diabetes mellitus was defined as documented prior history thereof or use of anti-hyperglycemic agents. LOS referred to the total duration in days the patient was a hospital inpatient during the acute admission at Hamilton General Spinal Cord Service and, whenever applicable, the inpatient rehabilitation admission.

2.3. Thromboprophylaxis

We also examined the intensity and duration of thromboprophylaxis. Low-dose LMWH included use of enoxaparin 40 mg daily, dalteparin 5000 units daily, fondaparinux 2.5 mg daily, or heparin 5000 units twice daily. Increased intensity LMWH was defined as enoxaparin 30 mg twice daily. Low-dose LMWH was sequentially combined with warfarin (international normalized ratio [INR] range of 2 to 3) in 5 patients.

2.4. Primary and secondary outcomes

The primary outcome was incidence of symptomatic, objectively verified DVT via venous Doppler ultrasound and/or PE diagnosed using computerized tomography pulmonary angiogram (CTPA) within 90 days. Secondary outcomes were major bleeding, all-cause mortality, and fatal PE. Major bleeding was defined according to the International Society on Thrombosis and Haemostasis recommendations [16]. Fatal PE was defined as objectively verified PE on CTPA or diagnosed on autopsy.

2.5. Statistical analyses

The association between different variables and the presence of VTE was investigated via univariable analyses using the Fisher's exact test. These variables included gender (male versus female), age (≤51 years versus >51 years), body weight (<100 kg vs ≥100 kg), year of injury (2009 to 2011 versus 2012 to 2015), presence of leg paresis versus no neurological impairment, SCI with versus without injury, SCI with additional sites of injury versus spinal only, level of injury (cervical vs others), short versus long duration of hospital stay (≤79 days versus > 79 days), and low-dose LMWH versus increased intensity LMWH. The effect sizes are reported as odds ratios (ORs) with 95% confidence intervals (95% CIs). Other levels of injury include thoracic, lumbar, and ≥2 levels.

Step-wise Cox modeling with forward selection analyses were also performed to identify independent risk factors for VTE. The effect sizes are reported as hazard ratio (HR) with 95% CI. These analyses were performed using the SAS, version 9.3.

For all analyses, the values of $p < 0.05$ were considered as indicative of statistical significance.

3. Results

A total of 151 consecutive patients with acute SCI met our inclusion criteria. Sixty patients were excluded: 34 patients had short hospital admissions (≤7 days), 17 were transferred to a different hospital location (median time of 11 days, range 5 to 29 days), 3 had another reason for admission, and 6 patients were already on therapeutic anticoagulation. The baseline characteristics of the patients are summarized in Table 1. Patients were followed for a median of 90 days (range, 1 to 90) and the median length of hospital stay was 79 days (range, 1 to 90).

Hundred and eleven patients (73.5%) had paraplegia or tetraplegia, 10 patients (6.6%) had no neurological impairment, and the degree of impairment was unspecified in 30 patients (19.9%). A total of 112 patients (74.2%) had traumatic SCI with a fracture, 34 (22.5%) had traumatic SCI without a fracture, and 5 (3.3%) had non-traumatic SCI. Ninety four patients (62.2%) had SCI alone versus 57 (37.8%) who had additional sites of injury. The majority of patients (52.3%, 79 of 151) had cervical SCI followed by thoracic (21.9%), ≥2 levels (15.9%), and lumbar SCI (9.9%).

The median duration of thromboprophylaxis was 65 days (range, 2 to 90) (Table 2). The majority of patients (59.6%) received low-dose LMWH either alone (85 of 151, 56.3%) or sequentially with warfarin (5 of 151, 3.6%) with INR range of 2 to 3 compared to 48 patients (31.8%) who received increased intensity LMWH, either alone (9 of 151, 6%) or sequentially with low-dose LMWH (39 of 151, 25.8%). Thirteen patients (8.6%) had no thromboprophylaxis. Of the 151 patients included, 29 (19.2%) were taking aspirin during the follow-up period.

Of the 151 patients enrolled, 17 patients (11%) had symptomatic VTE (9 PE, 6 lower extremity DVT, 1 upper extremity DVT, 1 with both DVT and PE, and nobody with fatal PE). The survival without a VTE is shown in Fig. 1. There was no statistical difference in the rate of VTE between low-dose LMWH group compared to those who received increased intensity LMWH (13.3% versus 8.3%, respectively; odds ratio [OR] 0.59, 95% CI, 0.13–2.1, $p = 0.58$).

The incidence and time to major bleeding or death are shown in Table 3. The cause of death in these patients included: 7 neurogenic shock (33.3%), 5 respiratory failure (23.8%), 3 sepsis (14.3%), 3 multifactorial (14.3%), 2 unspecified (9.5%), and 1 hemorrhagic shock (4.8%).

Table 1
Baseline characteristics.

Characteristics	Results
Age (median; range)	51 (17 to 91 years)
Males (N;%)	106 (70)
Aspirin use (N; %)	29 (19.2)
Co-morbidities (N;%)	
Hypertension	45 (29.8)
Diabetes	21 (13.9)
Coronary artery disease	5 (3.3)
Cerebrovascular accident	4 (2.6)
Cancer	7 (4.0)
Renal disease	2 (1.3)
Respiratory disease	21 (13.9)

N: number of patients.