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Symptomatic venous thrombo-embolism in low-energy isolated fractures in hospitalised patients

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ABSTRACT

Introduction: In the prevention of venous thrombo-embolic events (VTEs) in isolated low-energy fracture patients, management guidelines are conflicting and prior literature is lacking. We aimed to determine the incidence and factors associated with the development of symptomatic VTE in this patient cohort.
Materials and methods: To identify patients with isolated, low-energy fractures, we studied billing records from all admissions to our tertiary care orthopaedic hospital from 2007 to 2009. We used International Classification of Diseases, 9th Revision codes to identify patients who developed deep vein thrombosis (DVT) and/or pulmonary embolism (PE) during their hospital admission or within 90 days of discharge. We also collected data on socio-demographics, type of injury, fracture treatment, co-morbidities and anticoagulation therapy at time of admission. This study was a retrospective review of a database.
Results: In total, 1701 admissions fit our criteria. Average patient age was 64.27 years and 64.4% were female. There were 479 (28.2%) upper extremity fractures and 1222 (71.8%) lower extremity fractures. Incidence of clinically significant VTE was 1.4%. Of the 24 patients with 25 documented VTE, there were 13 DVTs and 12 PEs, including 2 fatal PEs (0.012%). Nineteen VTEs occurred in association with lower extremity fractures and six with upper extremity fractures; 74% of patients were chemoprophylaxed. Patients with VTE had an average age of 69.5 years and an average body mass index (BMI) of 28 kg m^{-2}. Logistical regression analysis found female sex ($p = 0.05$) and elevated BMI ($p = 0.003$) to be the only significant predictors of VTE.
Conclusions: Clinically significant VTE among patients who sustained isolated, low-energy fractures was found to be low in the setting of standard VTE prophylaxis. Our incidence was consistent with that of patients undergoing total hip arthroplasty. Female sex and increased BMI were statistically significant predictors of VTE.

Introduction

Venous thrombo-embolic events (VTEs), which include deep vein thrombosis (DVT) and pulmonary embolism (PE), are a source of morbidity and mortality among hospitalised populations. Although rare,[1] untreated PE carries a mortality rate of 30% and is related to between 5% and 10% of US inpatient hospital deaths.[2,3] Among orthopaedic patients, increased risk has been identified in those who sustained fractures of the hip, pelvis and spine as well as patients undergoing arthroplasty of the knee or hip. Patients hospitalised for such injuries can carry risk rates as high as 40–60% without VTE prophylaxis.[4,5] Chemoprophylactic therapy has been repeatedly demonstrated to significantly reduce the risk of thrombo-embolic complications following major high-risk procedures, including orthopaedic surgery.[6–11]

Current guidelines for managing VTE risk are contradictory.[12] The American College of Chest Physicians (ACCP) recommends providing guidance for prophylaxis in patients with either moderate or high risk for VTE as well as treatment with low-molecular-weight heparin (LMWH), fondaparinux or dose-adjusted vitamin K antagonists (VKAs) for elective arthroplasty as well as hip fracture surgery.[13] ACCP also recommends prophylaxis for high-risk patients undergoing knee arthroscopy.[4,13] Patients who have surgery durations of under 30 min, are younger than 40 years and undergo repair of minor fractures other than pelvis, hip or femur are considered low risk and are not explicitly recommended for VTE prophylaxis.[14] Since many orthopaedic surgeons consider the risk of bleeding to be significant for patients on therapeutic doses of anticoagulant agents, alternative methods of minimising

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risk have been investigated. The American Association of Orthopaedic Surgeons' (AAOS) guidelines for the prevention of symptomatic PE among patients undergoing total knee arthroplasty suggest the need to stratify risk of both VTE and bleeding complications.[15] Subtle differences between ACCP and AAOS recommendations have led to some inconsistencies in how hospital protocols have been implemented.[16] Furthermore, isolated extremity trauma is conspicuously absent from these guidelines for VTE chemoprophylaxis.

Lower extremity fractures distal to the hip have been studied prior to the adoption of prophylactic recommendations. The incidence for clinically occult DVT has been reported to be 28%, with the highest incidence in patients treated for tibial plateau and femoral shaft fractures. This study found age, time to surgery and longer operating times to be associated with a greater incidence of DVT.[17]

LMWH has been shown to reduce the total incidence of DVT for patients with fractures of the lower extremity treated with surgical fixation, but evidence is inconclusive regarding reduction of risk.[18] Therefore, physicians have been left to rely on anecdotal evidence and clinical judgement when managing post-fracture patients. As a result, adherence to ACCP guidelines and prophylactic protocols varies between individual institutions.[3] The purpose of this study was to identify the incidence of symptomatic VTE in patients who sustain low-energy isolated fractures. A secondary aim was to identify what injury and patient demographic factors are associated with the development of VTE.

Materials and methods

We conducted a retrospective study of a large cohort of patients admitted to our medical centre (non-trauma centre, academic hospital) over a 3-year period and analysed for potential modifying factors in the setting of standard DVT prophylactic protocols. Hospital billing records from 2007 to 2009 were used to identify patients according to International Classification of Diseases, 9th Revision (ICD-9) code for primary diagnosis on admission (Table 1). Patients were identified and included in the study if their primary diagnosis of admission was consistent with an isolated fracture of the extremity, pelvis or shoulder girdle. Patients younger than 18 years and patients who sustained multiple traumatic injuries were excluded.

Table 1
ICD-9 codes used in the analysis by fracture location.

Fracture location	ICD-9[a]	90-day outcome measures	ICD-9[a]
Pelvis	808	Pulmonary embolus	I26
Clavicle	810	Deep-vein thrombosis (all sites)	180.1–3, 180.8–9
Scapula	811	Death	512–512.9, 514–519.9, 797–799[b]
Humerus	812		
Forearm	813		
Carpal	814		
Hip	820		
Femur	821		
Patella	822		
Tibia/fibula	823		
Ankle	824		
Tarsal/calcaneus	825		

[a] International Statistical Classification of Diseases and Related Health Problems (9th Revision).
[b] Also includes deaths reported in discharge summary but not listed in billing records.

Hospital electronic medical records were used to access treatment information and patient data and socio-demographic information was collected on all identified patients. Information about the fracture location, treatment intervention and other injury was also included for analysis. Previously identified risk factors for VTE were included as study variables including age, sex and body mass index (BMI). Medical and co-morbid conditions including smoking history, diabetes, cancer, hyperlipidaemia, osteoarthritis and pre-existing anticoagulant therapy were used as variables for regression analysis.

Data were collected on patient chemoprophylaxis. No standard VTE prophylaxis was used in patients other than hip and pelvic ring fractures. In these cases only LMWH was prescribed by the orthopaedic service. Patients were considered chemoprophylaxed if they were treated with heparin, LMWH or VKAs. Patients who presented already on anticoagulant therapy for a pre-existing medical condition were considered to be prophylaxed on admission. If they were reversed for an operation they were considered anticoagulated if prophylaxis was restarted post surgery.

All patients who developed clinically symptomatic DVT or PE diagnosed by venous ultrasound or chest computed tomography during or within 90 days of discharge were included in the VTE group and time from initial injury to presentation with clinically significant VTE was collected. Clinically symptomatic DVT was defined as cases identified secondary to pain, swelling or other symptomatic changes necessitating diagnostic testing. These included DVTs at and below the knee. All were found secondary to clinical suspicion. We did not screen for DVT or PE.

Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at our institution.[19] REDCap is a secure, web-based application designed to support data capture for research studies.

Statistical analysis

We determined the incidence of symptomatic DVT, PE and overall VTE. To determine confounding factors, univariate comparisons between the VTE group and the non-VTE group were made based on the demographic data and operative parameters, including age, gender, BMI, DVT prophylaxis, time from initial injury to diagnosis of VTE, location of fracture and co-morbid medical conditions. We used chi-squared test for categorised data and Student's *t*-test for continuous data. For the variables with a p value < 0.1 in the univariate analyses, multivariate logistic regression analyses were performed. The independent variables tested for the multivariate logistic regression analyses include age, gender, etc. as confounding factors; the dependent variable was whether the DVT occurred postoperatively. From the multivariate regression analyses, it was assessed which variables were the risk factors for occurrence of DVT. Statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) for Windows statistical package (version 17.0; SPSS, Chicago, IL, USA).

Results

Between 2007 and 2009, 1701 adult patients were admitted to our medical centre with the diagnosis of a low-energy, isolated fracture. The mean age of this cohort was 64.27 (18–101) years; 1096 (64.4%) of the patients were female and 605 (35.6%) male. The average BMI was 26 kg m^2. As many as 1222 (71.8%) fractures were in the lower extremity and 479 (28.2%) in the upper extremity. The most common fracture site was the hip (femoral neck, intertrochanteric and subtrochanteric), accounting for 518 (30.5%) fractures. The most common upper extremity fracture was the humerus, with 237 (13.9%) (Table 2).

Overall, 24 patients were diagnosed with 25 clinically significant VTE. The incidence for symptomatic VTE was 1.47%. There were 13 DVTs and 12 PEs. Among upper extremity fractures, there were six VTEs (1.25%). These include two PEs, one in a patient with a distal humerus fracture and one with a clavicle fracture, and four DVTs, in patients with a distal radius fracture, a humeral shaft fracture, a proximal humerus fracture and a clavicle fracture. Only the distal radius fracture and the clavicle fracture with PE did not receive chemoprophylaxis. Of note, the distal radius and humeral shaft fracture patients with DVT had a previous history of PE. Nineteen VTEs (1.75%) occurred among lower extremity fractures. Seventeen VTEs (2.6%) occurred in association with hip and pelvis fractures. The incidence of VTE among all other fractures was 0.7%. Two patients (0.012%) expired following PE, while the all-cause mortality rate was 0.81%. PE was associated with 14.3% of all inpatient deaths (Table 3).

Among the patients who developed VTE, 75% were women. The average age was 69.5 years. The average BMI was 28 kg m^2. The average time from initial injury to diagnosis of VTE was 10.26 days (range 0–77 days).

Logistical regression analysis identified female sex ($p = 0.05$) with an odds ratio of 1.01 and BMI ($p = 0.01$) with an odds ratio of 1.11 as significant predictors of development of VTE. There was no difference in the development of VTE between upper and lower extremity fractures (Table 4).

A logistical regression analysis was performed to find significant predictors of chemoprophylaxis among covariates. Approximately 74.3% of all fractures treated received chemoprophylaxis with LMWH, heparin or VKAs. This percentage was much higher among lower extremity fractures, with 85.6% treated. Upper extremity fractures were prophylaxed 45.3% of the time. This difference was found to be statistically significant. Chemoprophylaxis was reported for 94% of patients with hip or pelvis fractures. All other fracture types were given chemoprophylaxis 66% of the time. All patients on pre-existing anticoagulation with agents such as Coumadin were considered as equivalent to being prophylaxed if they were continued on their regimens. Twenty-one patients who developed VTE following admission had received DVT prophylaxis from time of presentation for a 1.7% incidence of VTE among the 1264 patients treated with chemoprophylaxis. Four VTEs in three patients were found to be symptomatic upon presentation to the hospital or prior to surgical intervention. This was consistent with a 0.9% incidence of VTEs among the 437 patients not treated with chemoprophylaxis.

Table 2
Demographics of patients.

Number, *n*	1701
Mean age (SD)	64.27 (20.44)
Sex	
Male (%)	605 (35.6)
Female (%)	1096 (64.4)
BMI (average) (kg m^{-2})	26
Fracture location	
Clavicle	29
Scapula	15
Humerus	237
Forearm	194
Carpal	4
Pelvis	129
Ankle	280
Patella	50
Tibia/fibula	127
Tarsal/calcaneus	58
Hip	518
Femur	60
Anticoagulant medication[c]	
Yes	344 (20.2)
No	1217 (71.5)
Comorbidities	
Diabetes	216
Hyperlipidaemia	368
Cancer	207
OA	138
Treatment type	
Non-op (%)	221 (13.0)
Ex-fix[b] (%)	5 (0.3)
ORIF[a] (%)	1112 (65.4)
Other (%)	253 (14.9)
DVT chemoprophylaxis	1264 (74.3)
Upper extremity	217 (45.3)
Lower extremity	1043 (85.6)

[a] Open reduction-internal fixation.
[b] External fixation.
[c] Patients on anticoagulation for other medical condition at time of admission.

Discussion

Virchow's triad of venous stasis, vascular endothelial injury and hypercoaguability has the potential to increase the risk of clot formation.[4] To date only patients who have sustained fractures of the hip, open fractures of the lower leg or major trauma including the spinal cord are considered at major risk for VTE.[20] Much of the population seen by an orthopaedic specialty service at a major medical centre will be defined as greater than minimal risk. According to ACCP guidelines, those patients with moderate or high risk must be given prophylaxis unless they posses absolute contraindications.[21] Studies have shown that even with ACCP guidelines in place, chemoprophylaxis often goes underutilised.[22]

We determined that the incidence of clinically significant VTE among our large population of low-energy isolated fracture patients was similar to that documented in the literature for patients undergoing total hip arthroplasty with appropriate DVT prophylactic treatment. Within our population DVT prophylaxis was administered to approximately three-quarters of all fracture patients. Patients with upper extremity fractures received chemoprophylaxis less than half of the time. This is likely due to physicians following ACCP guidelines that stratify these patients as low risk for developing PE (low risk defined by surgery duration of <30 min, age < 40 years and repair of minor fractures other than pelvis, hip or femur; all other fractures are therefore moderate to high risk).[14] Prophylaxis rates were highest for patients with fractures classically associated with the greatest risk (hip and pelvis). Our incidence reflects VTE occurrence in a large hospitalised population of orthopaedic patients when available DVT chemoprophylactic strategies are employed for patients exhibiting moderate to high risk.

Regression analysis demonstrated that factors previously associated with high rates of VTE incidence did not provide statistically significant prediction of these outcomes. Within our population it was not possible to detect a significant difference in outcomes associated with well-known risk factors such as age, smoking history, cancer history or surgical intervention. This likely shows that widespread use of DVT prophylaxis confounds these risk factors. However, it is possible that the low incidence of VTE did not allow for our study to reach significance.

While there were three DVTs and one PE among the 437 patients who did not receive chemoprophylaxis, this was not found to be statistically significant. VTE did occur in patients considered at low risk according to current guidelines, including six upper extremity patients. Fractures of the pelvis, hip or lower leg (with prolonged immobilisation) are considered as high risk according to ACCP and were associated with a higher incidence of VTE in our population; however due to small numbers of low-risk patients with adequate data, we were unable to determine a statistically significant difference. Although VTE occurred despite prophylaxis, and there was a higher incidence of VTE in patients receiving

Table 3
Complications following surgery.

		Total, *n* (%)	Upper extremity, *n* (%)	Lower extremity, *n* (%) (including hip/pelvis)
DVT[a]		13 (0.076%)	3 (0.63%)	10 (0.82%)
Non-fatal PE[b]	10 (0.059%)	2 (0.42%)	8 (0.65%)	
Fatal PE[b]		2 (0.012%)	1 (0.21%)	1 (0.082%)
Total VTE[c]	25 (1.47%)	6 (1.25%)	19 (1.55%)	
All cause mortality	14 (0.82%)	1 (0.21%)	13 (1.06%)	

[a] Deep-vein thrombosis.
[b] Pulmonary embolism.
[c] Venous thromboembolism.

treatment, it is inappropriate to conclude that chemoprophylaxis is ineffective at preventing VTE. Patients who received prophylaxis were higher risk patients at baseline, as this group included patients with high-risk fractures of the hip and pelvis. Given this patient population, it is possible that the VTE rate in the patients treated with chemoprophylaxis would have been higher if they had not received treatment. While both utilisation of prophylactic therapy as well as upper versus lower extremity injuries were shown to have insignificant differences in outcome in our study, more investigation needs to be done, including prospective studies, in order to further evaluate for potential improvements in protocol.

Goel et al. also looked at the incidence of DVT in a randomised controlled trail of 238 patients with unilateral below-the-knee fractures requiring operative fixation, with 127 in the LMWH group and 111 in the saline placebo group.[23] The primary end point was the difference in the incidence of DVTs detected by bilateral lower limb venography performed at the end of the 14 days of treatment. Eleven (8.7%) and 14 (12.6%) DVTs were found in the LMWH and placebo groups, respectively. They did not find a statistically significant reduction in the incidence of DVT with the use of chemoprophylaxis, although they concede their study lacked the proper sample size to "exclude the possibility that LMWH could be beneficial."[23] They report a higher rate of DVT, although this may be explained by the screening of all patients at 14 days, leading to the detection of non-clinically significant DVTs. We agree with their statement that further multicentre trials will be needed to come to a conclusion regarding risk reduction with chemoprophylaxis in this patient population.

There are several limitations within our study. Since we were limited to patients who were admitted for care, it is possible that some patients with isolated fractures who were discharged from the emergency department and not admitted were missed in this study. In addition, we only know about those patients who developed VTE in house or returned to our hospital with a VTE. It is possible that patients may have been admitted elsewhere for these complications and not captured. Many of these fractures would have been considered low VTE risk. Similarly, as this is a retrospective chart review, we are limited by charting that reflects what prophylactic therapy patients received. Additionally, because of the very low symptomatic VTE rate, we did not have sufficient patients to reach significance when comparing VTE in upper and lower extremity fractures. It will be worth noting how the ongoing transition to the electronic medical record impacts both the compliance with standard protocols as well as documentation.

Table 4
Logistic regression analysis for predictors of venous thromboembolic events.

Variables	Estimate	Standard error	Odds ratio[a]	*p* value
Female sex	1.26	−2.48	1.01	0.05
Age	0.21	0.01	1.01	0.75
BMI	0.04	0.11	1.11	0.01
Diabetes	1.17	−1.27	0.28	0.28
Smoke	4109.55	−15.91	<0.01	1
Hyperlipidaemia	1.12	−1.56	0.21	0.17
Cancer	0.66	1.11	3.04	0.91
Treatment type	0.407	0.19	1.2	0.64
Extremity	0.752	−0.123	0.89	0.87
Blood thinner	1.14	−1.19	0.15	0.1
Osteoarthritis	0.84	0.6	1.8	0.47

[a] Odds ratio adjusted for other variables in the model.

Conclusions

In conclusion, we found an overall incidence of symptomatic VTE of 1.47% in a large sample of low-energy community-acquired isolated fractures. There was a 1.25% rate of VTE in isolated upper extremity fractures. For hip and pelvis fractures the rate was 2.6% and 0.7%, respectively, for all others. Seventy-four percent of our patient population was given chemoprophylaxis for VTE while in the hospital. We had a death rate due to PE of 0.012%. Given the fact that upper extremity fractures have some incidence of VTE, a fact which has historically been ignored, perhaps prophylaxis should be considered in this patient population – especially in upper extremity fractures in women and overweight patients. Further prospective studies are warranted. This study provides a basis for larger, prospective multicentre studies looking at the prevention of VTE in this population.

Conflict of interest statement

None declared.

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